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CLINICAL EPIDEMIOLOGICAL STUDIES OF THE ASSOCIATION BETWEEN CHRONIC INFLAMMATION, IMMUNE-MODULATORY THERAPIES, AND CANCER

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CLINICAL EPIDEMIOLOGICAL STUDIES OF THE ASSOCIATION BETWEEN CHRONIC INFLAMMATION, IMMUNE-MODULATORY THERAPIES, AND CANCER

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Dedicated to, Tove, Folke and …

ABSTRACT

Rheumatic diseases are chronic conditions that affect a substantial proportion of the adult population. Likewise, cancer is a major threat to public health, and the leading cause of death worldwide. Chronic inflammation is a key component in both rheumatic disease and cancer, and during the last decades, major treatment advances have been made in both of these fields. Due to the high prevalence of cancer in the age groups typically affected by rheumatic disease, it is a common comorbidity. Disentangling the association between rheumatic disease and cancer is complicated by the fact that cancer risk and prognosis can be affected by both aberrations related to host defense in rheumatic disease, as well as the treatment. For example, we know that risk of lymphoma is directly linked to disease severity in RA, but this does not preclude a further risk increase by RA treatment. In this thesis we capitalized on the rich data sources of Swedish national registers. Patients with rheumatic disease and matched comparators were identified, and by linkage to other registers, treatments, comorbidities, and other data were added. This allowed for comparisons by treatment and other characteristics within patient populations, and let us benchmark risks to that of the general population.

Studies I and II investigated the risk of cervical neoplasia in RA, and SLE, respectively. In **Study I**, the aim was to assess if there was an increased risk of cervical neoplasia in RA overall, and if TNFi-treatment increased this risk. In **Study II** we wanted to investigate the risk of cervical neoplasia in SLE overall, and if this risk differed between treatment-defined subgroups. We tried to separate the risk associated with the respective disease itself, from that of any potential risk carried by immunosuppressant treatment of RA and SLE. In these studies, we considered factors which were associated with the exposure and the outcome, and could act as confounders of the risk of rheumatic disease/treatment on cervical neoplasia. We found that there was an increased risk of cervical neoplasia overall in both RA and SLE, and that these risks were further increased in subsets treated with TNFi in RA, and other immunosuppressants in SLE, although the extent to which this was a direct effect of the treatments was hard to disentangle. **Study III** investigated the risk of incident cancer, overall and by cancer site, in RA patients treated with TNFi and other bDMARDs. Five cohorts of RA patients initiating treatment with tocilizumab, abatacept, rituximab, and a first or second TNFi, were assembled, as well as a csDMARD treated cohort. With the exception of an increased risk of squamous cell skin cancer in abatacept-treated, there were no significant risk differences between bDMARD-, and csDMARD treated RA. We concluded that short- to medium-term use of tocilizumab, abatacept, rituximab, or TNFi drugs seems to be safe with regard to risks of incident cancer. **Study IV** investigated the association between RA and breast cancer, as well as anti-hormonal breast cancer treatment. In a matched cohort design, we replicated previous findings of a 20% decreased risk of breast cancer among women with RA. In a case-control design, we found that the risk of RA in women with breast cancer was also decreased. We found no evidence to support that anti-hormonal breast cancer treatment increased the risk of RA. Although we were able to take potentially important confounders into account, we could not disentangle the roots of the negative association between RA and breast cancer, which led us to conclude that it might be due to other shared factors.

LIST OF SCIENTIFIC PAPERS

I. Do RA or TNF inhibitors increase the risk of cervical neoplasia or of recurrence of previous neoplasia? A nationwide study from Sweden

II. Cervical neoplasia in systemic lupus erythematosus: a nationwide study

III. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice A Nationwide Cohort Study From Sweden

IV. Risk of breast cancer before and after rheumatoid arthritis, and the impact of hormonal factors

CONTENTS

LIST OF ABBREVIATIONS

ACPA	Anti–citrullinated protein antibody
AI	Aromatase inhibitors
ARTIS	The Swedish Biologics Register
CI	Confidence Interval
CRP	C-reactive protein
DAS28	Disease Activity Score of 28 joints
HAQ	Health assessment questionnaire
HR	Hazard ratio
HRT	Hormone replacement therapy
HSIL	High-grade dysplasia
ICD	International classification of diseases
LSIL	Low-grade dysplasia
NKCx	National Cervical Screening Registry
NMSC	Non-melanoma skin cancer
OR	Odds ratio
PIN	Personal identity number
PDR	Prescribed Drug Register
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
SRQ	Swedish Rheumatology Quality Register
TNFi	Tumor necrosis factor inhibitors
TNM	TNM Classification of Malignant Tumors

1 BACKGROUND

1.1 INTRODUCTION

Rheumatology is a field of medicine that involves the treatment of rheumatic disease, i.e. inflammatory joint disease and inflammatory systemic disease. The immune system protects the host from foreign pathogens, such as bacteria, viruses or parasites. Autoimmune conditions originate from an abnormal immune response, where the host reacts by attacking itself. This results in ensuing, often chronic, inflammation. In rheumatic disease, most parts of the body can be affected, but often it involves the musculoskeletal system, such as the joints. The chronic inflammation can cause pain and swelling, and, especially if left untreated, chronic disability and premature death. Chronic inflammation and immunity is also a key component in cancer development (1). Untreated inflammation and immunological aberrations in rheumatic disease might thus promote tumorigenesis. Conversely, treatment of rheumatic disease, which typically involves suppression or modulation of the immune system, can lower host defense against incipient tumors. Some of the agents used in rheumatology are also used in the treatment of certain forms of cancer, but can themselves be associated with increased cancer risks (2, 3).

1.2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that typically affects the small joints in hands and feet. In Sweden, the incidence is about 41 cases per 100,000 person years with a marked female predominance (4). The debut is often insidious, with fatigue, morning stiffness, and symmetrical joint pain and swelling of the small distal joints. Although symptoms arising from local inflammation in the joints is the most prominent feature, RA is a systemic disease. Constitutional symptoms e.g. fever, malaise, and weight loss, are common and arise from systemic inflammation. Other extra-articular manifestations, such as serositis, and cutaneous vasculitis, also feature in RA (5). While advances in understanding the pathogenesis of RA have been made, the etiology is still unclear. Autoimmunity, as demonstrated by antibodies against anti-citrullinated proteins (ACPA), can predate clinical symptoms of RA by decades (6, 7). Identified genetic factors include an association with human leukocyte antigen DR4, and the heritability of RA has been estimated at about 40%, with a higher heritability for ACPA-positive RA (8). Cigarette smoking doubles the risk of developing RA, and is particularly associated with ACPA-positive RA, while other environmental risk factors are not well established (9-11). Although laboratory analyses such as C-reactive protein (CRP), rheumatoid factor, and ACPA, help in diagnosing the disease, RA is still a clinical and criteria-guided diagnosis. The latest classification criteria aimed at facilitating early diagnosis of RA (12). Although treatment advances have been made, RA is a chronic disease that still causes much suffering and disability. Patients with RA are at increased risk of several comorbid conditions, most importantly cardiovascular disease, but also certain types of malignancies and infections (13). These conditions contribute to the increased mortality that is still present in RA. (14).

1.3 SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that primarily affects women. The prevalence in Sweden is approximately 46 to 85 per 100,000 adults (15). The phenotype of SLE varies from mild disease, mainly affecting skin and joints, to severe organ destructing disease. Analogous to RA, there are no diagnostic criteria, but classification criteria developed for research purposes can help in diagnosing the disease (16). Organs that are often involved in SLE include joints, skin, kidneys, lungs, heart, the central nervous system, and the circulatory system. The diverse clinical presentation of the disease can pose a challenge to the clinician in both diagnosis and treatment. Furthermore, SLE is associated with several comorbidities, e.g. cardiovascular disease, cancer, osteoporosis and infections (17, 18). The etiology of the disease is not clear but is known to involve genetic factors, the heritability has been estimated at 45%, similar to that of RA (19). Environmental risk factors such as sunlight exposure, EBV infection, and smoking have also been identified (20, 21). SLE is associated with the production of many autoantibodies. Antinuclear antibodies are present in more than 90% of patients, among these the highly SLE-specific anti-double-stranded DNA antibodies present in 70% of SLE-patients, but only in 0.5% of healthy controls (22). Apart from these antibodies, SLE is associated with numerous immunological aberrations involving both innate and adaptive immunity (23). The fact that SLE is much more common in women than men, and that it often presents during the reproductive years, suggests that hormonal factors might be involved. This was supported by a randomized controlled trial (RCT), which showed that women given hormonal replacement therapy (HRT) were more likely to experience flares of the disease, although the flares were mostly mild (24). Also, the Nurses' Health Study found that hormonal factors such as early age at menarche, oral contraceptive use, early age at menopause, and HRT were all risk factors for developing SLE (25). Furthermore, as opposed to women with RA, women with SLE often experience a flare during both pregnancy and the puerperium (26).

1.4 TREATMENT

The current paradigm in the treatment of RA is that aggressive treatment should be introduced early and then be escalated in pursuit of clinical remission. We have no means of healing damaged joints, but if disease progression can be halted at an early stage, joint damage and disability can be prevented. Pharmacological treatment of RA mainly involves so called disease modifying anti-rheumatic drugs (DMARDs), corticosteroids, and non-steroidal inflammatory drugs (NSAID) (27). Systemic corticosteroids are effective in reducing inflammation and relieving symptoms, and may halt disease progression, but are associated with numerous side effects. They are therefore often part of the initial treatment strategy, and used as bridge-therapy or to treat flares, but the goal is to minimize the use of these agents. DMARDs decrease inflammation and slows disease progression as measured radiographically. Traditional small molecule DMARDs including agents such as methotrexate, sulfasalazine, and hydroxychloroquine, will from here on be referred to as conventional synthetic DMARDs (csDMARDs). Methotrexate is the anchor in RA therapy and is used as monotherapy, or in combination with other DMARDs and steroids. Targeted

protein DMARDs, such as tumor necrosis factor inhibitors (TNFi), rituximab, abatacept, tocilizumab, will be referred to as biologic DMARDs (bDMARDs).

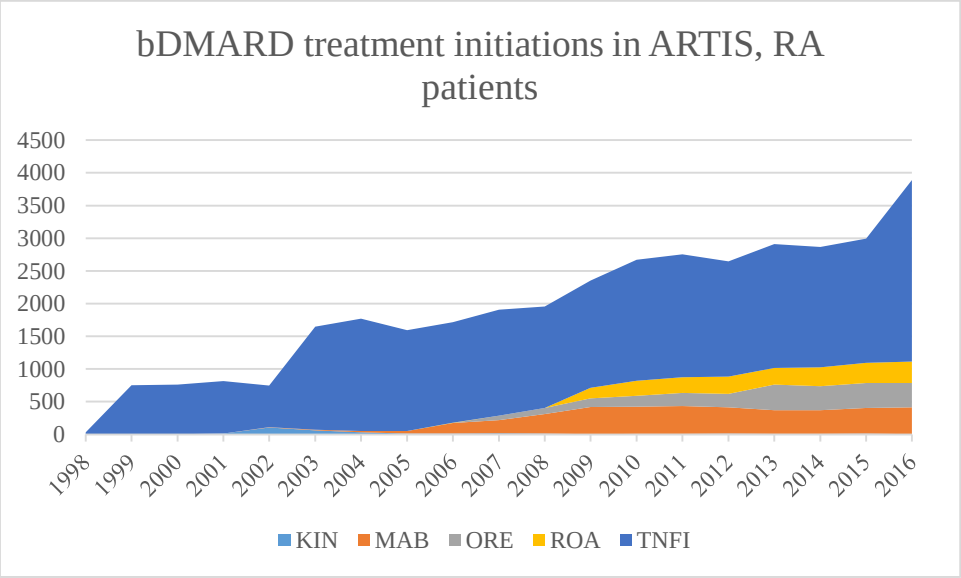

Figure 1.1. Number of registered bDMARD treatments initiated in RA patients in the Swedish Biologics Register (ARTIS) by year. KIN=Kineret (anakinra) MAB=Mabthera (rituximab) ORE=Orencia (abatacept) ROA=Roactemra (tocilizumab) TNFI=Tumor necrosis factor inhibitors

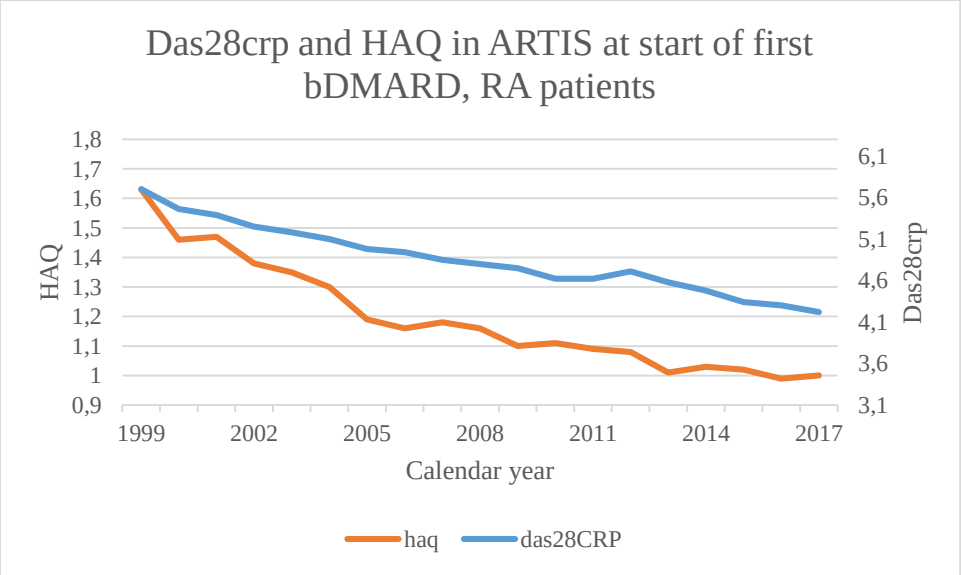

Figure 1.2. Disease activity score (DAS28-CRP) values and health assessment questionnaire (HAQ) values for RA patients registered in Swedish Biologics Register (ARTIS) at start of first bDMARD.

The introduction of bDMARDs in the late 1990's has revolutionized the treatment of RA due to their ability to alleviate symptoms and slow radiographic progression. They are often used as a second-line therapy if the patient has not responded to csDMARD therapy, or first-line therapy in patients with high disease activity and unfavorable prognostic factors, and often in combination with a csDMARD such as methotrexate (27). TNFi were the first, and are the most widely used agents of the bDMARDs. TNFi has been linked with an increased risk of serious infection and tuberculosis (28-31). Therefore, screening for tuberculosis and hepatitis,

and treatment of latent tuberculosis infection, is recommended before start of TNFi therapy. Further pre-treatment assesments before initation of bDMARD therapy typically includes full blood count, as well as both kidney- and liver function,

As mentioned, there is no reliable biomarker to diagnose RA. Likewise, there are no specific biomarkers to monitor disease activity. Besides clinical assessment and the patients self-reported degree of well-being, a couple of tools have been brought forward to aid clinicians. The disease activity score-28 (DAS28), is a score that incorporates the number of tender and swollen (based on 28 pre-specified joints), patient self-assessment of disease activity, and laboratory markers (either erythrocyte sedimentation rate or CRP). A health assessment questionnaire (HAQ), is a score that includes questions concerning activities of daily life (32). These two scores are used to monitor disease activity and guide clinicians in treatment decisions, and are frequently used as endpoints in clinical studies.

Table 1.1. Name and proposed mechanism of action for pharmaceutical agents discussed in this thesis

Name	Target/Proposed mechanism
bDMARDs	
Abatacept	CTLA4-Ig
Adalimumab	Anti-TNF α
Anakinra	Anti-IL-1
Certolizumab pegol	Anti-TNF α
Etanercept	Anti-TNF α
Golimumab	Anti-TNF α
Infliximab	Anti-TNF α
Rituximab	Anti-CD20
Tocilizumab	Anti-IL-6 receptor
csDMARDs and others	
Azathioprine	Purine synthesis inhibitor
Chloroquine phosphate (anti-malarial)	Suppression of IL-1, induce apoptosis of inflammatory cells and decrease chemotaxis
Ciclosporin	Calcineurin inhibitor
Cyclophosphamide	Alkylating agent
Methotrexate	Purine metabolism inhibitor
Gold salts	Unknown
Hydroxychloroquine (anti-malarial)	Suppression of TNF-alpha, induce apoptosis of inflammatory cells and decrease chemotaxis
Leflunomide	Pyrimidine synthesis inhibitor
Mycophenolate mofetil	Purine synthesis inhibitor
Sulfasalazine	Suppression of IL-1 & TNF-alpha, induce apoptosis of inflammatory cells and increase chemotactic factors
Tacrolimus	Calcineurin inhibitor

Pharmacological treatment of SLE mainly involves antimalarials, corticosteroids, csDMARDs, NSAIDs, bDMARDs (rituximab and belimumab), and other immunosuppressant drugs (33). The multifaceted clinical presentation of SLE is reflected in its treatment. Some patients that are in remission don't need any maintenance treatment, other patients receive maintenance treatment with e.g. antimalarials or corticosteroids, while

patients that are experiencing severe flares may need potent immunosuppressant therapy. The treatment is generally chosen by which organ systems that are affected, and the perceived urgency in treating these manifestations. For example, joint manifestations are common in SLE, but if nephritis is present at the same time, treatment will be guided by the nephritis. Corticosteroids are effective in reducing inflammation, and are widely used both in the treatment of flares, and as maintenance therapy. However, long-term treatment with corticosteroids is associated with severe side-effects, and therefore the lowest possible dose, if any, is the target. Antimalarials are especially effective against skin, and musculoskeletal disease manifestations, but are also equipped with other positive long-term outcomes, and reduce the need for corticosteroids even in patients with more severe SLE. They are therefore often recommended to all SLE patients if there are no contraindications.

1.5 **CANCER**

Cancer is a group of diseases that are caused by mutations in genes that alter the function or expression of genes that regulate key processes in in the cell, such as growth, survival and senescence. These mutations are passed on to daughter cells upon cell division, and cancer cells are thus subject to natural selection. The hallmarks of cancer were defined by Hanahan et al. in 2000 as 1) self-sufficiency in growth signals 2) lack of response to growth inhibitory signals 3) evasion of apoptosis 4) the ability to replicate without limits 5) development of blood vessels 6) invasive ability 7) metabolic pathway reprogramming 8) immune system evasion (34).

In Sweden, the life-time risk of developing cancer before the age of 65 is about 15%, rising to 30% before the age of 75 (35). Although site-specific rates differ, the overall incidence in men and women is quite similar. The most common cancers are prostate cancer and breast cancer, followed by skin, colon, lung, and bladder cancer (35). Although treatment advances have been made, cancer is in many cases still a deadly disease.

A large body of evidence supports the association between chronic inflammation and cancer. Many chronic inflammatory conditions are known to predispose the organism to cancer development (1). The etiological agents are in many cases infectious, such as human papilloma virus (HPV) infection in cervical cancer, or Helicobacter Pylori in stomach cancer. In other cases, the inflammatory state is caused by inhalation or ingestion of a chemical agent, such as in cigarette smoking and lung cancer. The immune system is needed by the tumor to create a suitable microenvironment in which to grow. Inflammatory cells promote the growth of blood vessels and supporting tissue. Furthermore, the immune system is essential in checking the development of cancer, and thus immunosuppression has been shown to promote the development of cancer. For example, recipients of a solid organ transplant, as well as HIV-positive patients, have an increased risk of many types of cancer (36).

1.6 RHEUMATOID ARTHRITIS AND CANCER

Before examining risks with different anti-rheumatic therapies, an understanding of the baseline risk of cancer in RA is important. However, the fact that most patients receive some kind of immunosuppressant or immunomodulatory therapy makes it hard to determine the baseline risk. The risk of cancer in RA is thought to be modified by factors relating directly to autoimmunity and inflammation, pharmaceutical treatment of RA, and environmental factors shared between RA and cancer e.g. as in the case of lung cancer. The overall risk of cancer in RA is elevated by about 5-15% compared to the general population, although the site specific data show a heterogeneous picture with both increased and decreased risks (14, 37-39). At the typical age of RA onset (~60 years), 9% will already have a cancer in their medical history, and more than 20% will develop a cancer in the following 15 years (35). Considering the high life-time risk of developing a tumor, the high prevalence of rheumatic disease, and the high mortality associated with many cancers, cancer constitutes a clinically highly relevant field in RA.

If we turn our attention to site-specific cancers, malignant lymphoma is the most clearly linked cancer, the relative risk is about doubled, but the risk has been shown to be directly linked to the disease activity in RA (40). The risk of lung cancer has been estimated to be increased by about 60%, this might be partially explained by the increased risk of RA in smokers. However, a large case-control study found an increased risk of lung cancer in patients with RA even when adjusting for smoking and asbestos exposure (41). As for melanoma, there is a reported 25% risk increase in RA (14). Regarding non-melanoma skin cancers, there seems to be a 50% increased risk in RA (42-45). However, as mentioned, decreased risks has also been reported. For colon cancer, the previously mentioned meta-analysis by Simon et al. found a standardized incidence ratio (SIR) of 0.78 (95% confidence interval, CI 0.71-0.86) (46). It has been hypothesized that this might be due to prolonged use of NSAIDs in RA.

Concerning the risk with csDMARD treatment, azathioprine has been linked to an increased risk of lymphoma in RA (40). This may, at least in part, be due to channeling bias. Solomon et al. found an increased risk of cancer among RA patients treated with methotrexate compared to those treated with other csDMARDs or TNFi (47). Methotrexate, which is also used as a chemotherapeutic agent, has been associated with a slightly increased risk of non-melanoma skin cancer (NMSC) (48). However, most studies have found no such associations (49, 50). Cyclophosphamide, a drug mostly used in extra-articular RA, has been linked with an increased risk of several cancers (51, 52). Lastly, glucocorticoids which are widely used in RA, have been associated with an increased risk of both overall cancer (53), and NMSC (54). Although there does not seem to be a clear association between disease severity and the overall risk of cancer in RA (44, 55), it might be an important confounder of these site-specific results.

1.7 **BDMARDS AND RISK OF CANCER**

TNF was first identified in 1975 for its ability to induce rapid hemorrhagic necrosis of experimental malignant tumors (56). It was soon discovered that TNF was a powerful regulator of the immune system, and that the anticancer properties of the cytokine were just one of its abilities. In 1987 it was found that TNF could stimulate tumor growth by inducing angiogenesis (57). This and subsequent discoveries of TNF as a mediator of cancer-related inflammation showed that TNF could be both pro- and anti-carcinogenic. Thus when TNFi therapy was introduced in the late 90's, there were well-founded uncertainties about how these drugs might affect carcinogenesis, tumor progression, and tumor relapse. The issue of drug safety was one of the key reasons clinical registers, where patients treated with TNFi (and later other bDMARDs) could be followed longitudinally, were established in various countries (58, 59). Clinically, questions such as which treatment should be offered to patients with a previous cancer, or if certain categories of patients should be screened for certain cancers, are commonplace.

An early meta-analysis of RCTs by Bongartz et al. found a three-fold increased risk of cancer, which was dose dependent, in adalimumab-, and infliximab- treated RA (60). Limitations included possible confounding, and relative small numbers (three events in the placebo group) partly due to short follow-up (about three- to twelve months), and comparisons did not take person-time into account. Nevertheless, the worrisome results of the study had a great impact, and later a separate meta-analysis of etanercept RCTs also showed an increased, although statistically non-significant, risk of cancer compared to placebo (61). However, subsequent meta-analyses that have included many RCTs, including other indications than RA, have not revealed any increased risks of overall cancer with TNFi compared to csDMARDs or placebo, although Askling et al. reported a higher risk of NMSC (62, 63).

Data from observational studies have mainly been reassuring. A meta-analysis, which mostly consisted of data from the large European biologics registers, found no increased risk of overall cancer, with a pooled estimate of 0.95 (95% CI 0.85-1.05) (64). Similarly, observational studies based on data from the US (65), Taiwan (66), and Japan (67), have found no association, or decreased risks, of overall cancer among TNFi-treated RA. Thus most of the evidence point towards no increased risk of the overall short- and medium-term risk of cancer with use of TNFi. TNFi is also used in other autoimmune conditions, but the evidence in terms of cancer risk is sparse compared to that of RA. A Danish register study found no significant association between TNFi and overall cancer in inflammatory bowel disease (68) A study from the British biologics register found no association between TNFi and overall cancer in patients with psoriatic arthritis, although a higher risk of NMSC was reported (69).

Seeing as TNF has been used in the treatment of melanoma, there could be well-founded concerns about the effect of TNFi on the risk of melanoma (70). Indeed, signals of an increased risk of invasive melanoma with TNFi therapy arose early from both observational

studies and meta-analyses of RCTs (43, 71). A study from the Swedish Biologics Register (ARTIS) found that RA patients treated with TNFi have a 50% increased risk of invasive melanoma compared to bDMARD-naïve RA, although there was no increased risk of in situ melanoma (72). However, a large collaborative effort that collated data from several European registers, including ARTIS, could not confirm an increased risk of invasive melanoma among RA patients treated with TNFi (73).

Wolfe et al. found a 50% increased risk of NMSC among bDMARD-treated (almost exclusively TNFi) RA patients compared to RA patients not treated with bDMARDs (71). This finding was not confirmed in two later studies from the Danish, and the British, biologics registers, where no statistically significant risk differences was observed comparing TNFi-treated RA patients versus non-treated, although 50-100% risk increases was observed for TNFi vs. the general population (43, 74). A study from ARTIS reported a doubled risk for squamous cell skin cancer in biologics-naïve RA, and a further 30% risk increase among TNFi-treated RA patients, but found no increased risk for basal cell skin cancer (75). Apart from skin cancer, TNFi has also been linked with an increased risk of lymphoma (76). However, most studies have shown no such association (64, 77). Since RA disease activity has been shown to be a risk factor for lymphoma, drug safety studies in RA with lymphoma as the outcome might be particularly susceptible to channeling bias.

For bDMARDs other than TNFi, considerably less is known about the risk of cancer. These agents target different pathways in the immune system which could theoretically lower host surveillance against incipient tumors, or accelerate tumor progression. Abatacept is a CTLA-4 fusion protein which inhibits the co-stimulatory signal from antigen-presenting cells (78). A pharmaceutical agent with essentially the opposite mechanism i.e. a CTLA-4 blocker, ipilimumab, is approved for the treatment of malignant melanoma (79), a fact which could prompt some concerns about the safety of abatacept in terms of risk of melanoma. Nevertheless, pooled data from RCTs (including open-label extensions) have not shown any increased risk of cancer among RA patients treated with rituximab, abatacept, or tocilizumab. (80-82). However, RCTs are often small, more suited to studying short-term risks, and often use narrow inclusion criteria which excludes large groups of patients, e.g. patients with comorbid conditions such as a previous cancer. Therefore, observational studies should be more suited to studying the medium to long term risk of cancer with bDMARD therapy. On the other hand, observational studies have inherent limitations as well. Confounding and channeling bias is an obvious issue, especially since bDMARD therapy is often reserved for patients with more severe disease, patients that have failed other therapies, or patients with various comorbid conditions. Prior to the studies in this thesis, only a few observational studies had been published on the subject of non-TNFi bDMARDs and cancer, with mostly reassuring results (48, 83, 84).

In Sweden, patients with RA are recommended to adhere to the national screening guidelines for cancer. A cancer in the medical history before treatment initiation, or the detection of a new tumour during ongoing treatment, may impact the choice of treatment in RA. For

example, The American College of Rheumatology recommends choosing a csDMARD over bDMARD in patients with a history of skin cancer (both melanoma and non-melanoma), and not choosing TNFi in patients with a history of a lymphoproliferative malignancy (85). Indeed, real-world data have shown that relatively few patients with a recent history of cancer receive treatment with TNFi (86). Channeling of patients with cancer in the medical history away from TNFi therapy highlights the clinical relevance of risk for cancer recurrence with TNFi. Previous observational studies on head and neck cancer (87), breast cancer (88), and overall cancer (89-92), have not shown an increased risk of cancer recurrence with TNFi therapy. However, these cancer recurrence studies are often low powered and, as previously stated, subject to channeling bias.

1.8 **CERVICAL CANCER**

Worldwide, cervical cancer is the fourth most common cancer in women affecting more than 500,000 women per year (93). With a few rare exceptions, invasive cervical cancer is caused by persistent HPV infection, via low-, and high-grade dysplasia (94). Most often cervical cancer develops from squamous cell epithelia, but 10-20% are derived from glandular epithelia (95). Both premalignant squamous and glandular cells can be graded according to their malignant potential. In this thesis I will use the term *low-grade dysplasia* (LSIL) for mild dysplasia of either squamous or glandular origin (including cervical interaepithelial neoplasia grade 1, and atypical glandular cells), and *high-grade dysplasia* (HSIL) for moderate or severe dysplasia of either squamous or glandular origin (including adenocarcinoma in situ, cervical carcinoma in situ, cervical interaepithelial neoplasia grade 2 and 3). Although most sexually active women will be infected by HPV at some point in their lives, only a fraction of infections become persistent, and even fewer develop invasive cancer. The aim of cervical screening program is to detect pre-cancerous lesions before they develop into invasive cervical cancer, and also to detect invasive cervical cancers at an earlier clinical stage. Cervical screening traditionally involves a Papanicolaou smear test, or "pap smear", named after the Greek doctor that invented it in the early 20th century. Cells around the transformation zone of the cervix are sampled and examined under a microscope. If abnormal cells are detected, a subsequent colposcopy can be performed. Colposcopy visualizes the cervix and allows for biopsies to be taken for further histopathological examination. Since it was discovered that HPV causes cervical cancer, HPV testing has been introduced as an alternative, and a complement, to pap smear testing. The Swedish cervical screening program invites all women resident in Sweden to be screened every three years between the ages of 23-50, and every five years between the ages of 50-64 (previously 50-60). Apart from pre-planned screening conducted within the framework of the national screening program, a substantial proportion of cervical screening results from opportunistic screening. Opportunistic screening is screening carried out, typically by a midwife or a gynecologist, during a regular check-up, or because of alarming symptoms such as vaginal bleeding. Organized, pre-planned screening, is considered more effective than opportunistic screening. Higher coverage is achieved when women are invited instead of taking the initiative themselves. Also, pre-planned screening can optimize the timing between the tests,

in terms of both protection and cost-effectiveness. Since the introduction of organized cervical screening in the 1960s, there has been a dramatic decrease in the incidence of cervical cancer (96). At the same time the incidence of cervical carcinoma in situ has increased due to earlier detection. Further decreases in the incidence of cervical cancer are expected with the introduction of HPV vaccines on the Swedish market in 2006, and an organized vaccination program of Swedish girls in 2012.

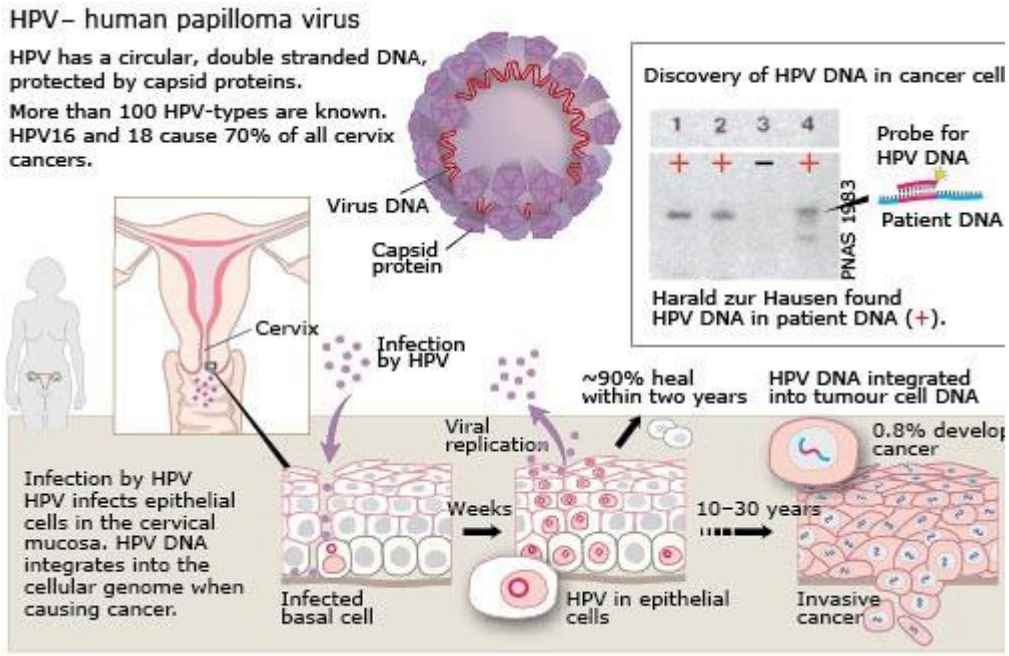

Figure 1.3. Illustration of the progression from initial HPV-infection to invasive cervical cancer. ©The Nobel Committee for Physiology or Medicine 2008, Illustration: Annika Röhl

Chronic inflammation and immunosuppression might impede host clearance of HPV infection, and thus increase the risk of cervical cancer. Therefore, the question if there is an increased risk of cervical cancer, either due to the disease itself or the associated treatments, has attracted interest in both RA and SLE. An observational study based on American healthcare claims databases found a 50% increased risk of high-grade dysplasia (CIN 2–3 or invasive cervical cancer) among bDMARD-naive women with RA compared to the general population (97). However, a large study based on the Californian Cancer Registry found a significantly decreased risk of cervical cancer among patients with RA compared to the general population (98). A meta-analysis by Simon et al. included 15 studies and found a pooled standardized incidence ratio of 0.87 (0.72, 1.05) compared to the general population. Thus there does not seem to be an increased risk of cervical cancer with RA per se (14).

An observational study with data from the Danish Biologics Registry (DANBIO) did not find any difference in risk for cervical cancer comparing arthritis patients that were bDMARD-treated with bDMARD-naïve (99). Two studies have been published on the risk of genital cancer among TNFi-treated women with RA with a history of cervical carcinoma in situ (100), and any premalignant lesion of the cervix (101). Although there were no events in the

TNFi-treated patients in either of the two studies, the number of patients included were too few (n=190 and n=233) to draw any firm conclusions.

Several studies have found an increased risk of HSIL among patients with SLE (97, 102). However, for invasive cervical cancer the picture remains unclear. Several studies have shown no significant risk increase in SLE (103, 104). A collaborative effort resulted in a multi-center study that found no increased risk (SIR 1.27 95%CI 0.78-1.93)(18). On the other hand, a large register-based study from California reported a lower risk among women with SLE compared to the general population (105). Of note, the same study reported higher rates of cancer of the vagina or vulva, which are also HPV-associated, among women with SLE.

Most of the studies on either SLE, or RA, and cervical cancer have not been able to consider important risk determinants, most importantly cervical screening. Whether women with SLE are appropriately screened for cervical cancer or not is not clear. On the one hand, patients who are already diagnosed with a severe chronic disease might be less inclined to screen for another disease. On the other hand, these patients are regular consumers of health care and might be reminded or referred to cervical screening in their regular contact with doctors and other health care professionals. Previous reports on SLE and cervical screening have found conflicting results, with both lower, and similar, rates of screening compared to the general population having been reported (103, 106). For RA, the degree of screening participation is also unclear, with both similar participation compared with the general population (103, 107), and suboptimal screening participation (108, 109), having been reported.

A multicenter study published in 2004 found that treatment with immunosuppressants among women with SLE was associated with subsequent abnormal Pap smears (110). Although the results were adjusted for important risk factors, disease activity was not included. A higher risk of dysplasia or cervical cancer among women with SLE might be due to either the disease itself or the potent immunosuppressants that are used to treat the disease. A potential risk increase associated with disease activity or disease severity would be hard to disentangle from different drug exposures.

1.9 **BREAST CANCER**

Breast cancer is the most common invasive cancer in women, both in Sweden and worldwide. Although it also occurs in men, the incidence is more than 100 times higher in women (35). Established risk factors for breast cancer include advancing age, early age at menarche, old age at menopause, HRT, exposure for ionizing radiation, family history of breast cancer, *BRCA1* or *BRCA2* mutations, alcohol, and high BMI, as well as protective effects of parity, breast feeding, and physical activity (111). Mammographic screening was introduced gradually in Sweden between 1974 and 1997 (112). The rationale for mammographic screening is that the mortality of breast cancer can be lowered by 16-25% by the earlier detection (113, 114), though this is still somewhat controversial (115). The current national screening program invites women between the ages of 40-74 to be screened every 18-24 months, and about 80% of invited women participate.

In the 1990's, observational studies published from Sweden and Denmark showed a lower risk of breast cancer among women with RA (44, 45). This finding was repeated in some later studies (42, 71), while others found no such association (49, 116). A meta-analysis of observational studies by Smitten et al. from 2008 (37), showed a 15% decreased risk of breast cancer in women with RA. The paper included studies from Denmark, Sweden, Japan, Canada, the UK, Spain, and the USA, and cohorts of both bDMARD-treated, and bDMARD-naïve patients. However, in the updated analysis by Simon et al. (117), 8 more recently conducted studies were added, and although the point estimate was very similar, there was no longer a statistically significantly decreased risk. Besides methodological differences, the study periods stretched from the 1960's to the 2000's, and therefore includes both women who were subject to mammographic screening and women who were not. Also the background risk of breast cancer in the populations varies by more than a factor of 5 between low risk countries such as Japan, and high risk countries such as the USA. A meta-analysis of cohort studies that was published in 2014 did not find a decreased risk of breast cancer in RA overall, but a decreased risk among women with RA in studies conducted on women in western countries, 0.82 (0.73, 0.93)(118). In studies conducted on women in Asia, instead an increased risk was reported 1.21 (95% CI 1.19-1.23). The authors point out that differences in breast density, an important risk factor for breast cancer, between different ethnic groups have been observed. However, a large Taiwanese study by Chen et. al included in both the meta-analysis by Simon et. al (46), and by Tian et. al (118), was heavily criticized by another Taiwanese study using the same data, for supposedly having miscalculated the SIRs (119, 120). Chen et. al is the only study that has reported an increased risk of breast cancer in RA, SIR=1.21 (95%CI 1.19–1.23), while the study by Huang et. al found an SIR of 0.90 (95%CI 0.78-1.03), more in line with previous studies.

A reduced risk of breast cancer among women with RA might be explained by the presence of shared risk determinants. Interestingly, a study by Hellgren et al. noted a lower prevalence of breast cancer even before RA diagnosis, indicating that this might be the case (121). However, it is unclear what these risk determinants might be. It has been hypothesized that this potentially negative association between breast cancer and RA is due to hormonal changes in RA (122). The incidence of RA in women during the reproductive years is more than twofold that of men, after which the differences between the sexes is attenuated (4). Also, women with RA often experience amelioration or remission during pregnancy, and a flare-up after delivery is common (123, 124). Most of the hormonal risk factors for breast cancer are not known as risk factors for RA. For example, among 28,000 women in the women's health initiative RCT, HRT was associated with an increased risk of breast cancer (125), but was not associated with developing RA (126). Likewise, parity is associated with a decreased long-term risk of breast cancer (127), but does not seem to be associated with the development of RA in general (128-130), although an increased risk of ACPA-negative RA has been reported in women of reproductive age (131). Long-term breast feeding seems to lower the risk of developing both RA (129, 130), and breast cancer (132). Current or recent use of oral contraceptives is thought to slightly increase the risk of breast cancer (133),

although it is probably dependent on the formula. Most studies investigating the relationship between use of oral contraceptives and development of RA have been unable to find an association (129, 130), although some have shown a protective effect (134, 135). However, early menopause, which is negatively associated with breast cancer (136), has been reported as a risk factor for RA, and in particular seronegative RA (130, 137, 138). Thus the relationship between hormones, breast cancer and RA does not seem straight-forward.

Another hypothesis is that the lower incidence of breast cancer among RA patients is due to a protective effect of aspirin against breast cancer (139). A modest risk decrease has been consistently observed in case-control and cohort studies (140), although a large RCT comparing low dose aspirin (and vitamin E) every other day vs. placebo showed no difference in risk of breast cancer with aspirin use (141). Lastly, the observed differences in risk might be due to protective effects of RA therapy, or differences in detection rather than true differences. Because breast cancer is detectable through physical examination and screening, and RA patients are high-utilizers of healthcare they may be more inclined to attend mammographic screening. A cohort study based on US commercial insurance data found higher rates of mammographic screening among women with RA compared to non-RA controls (107), although it is not self-evident that this finding is generalizable to countries with organized national mammography program.

Table 1.2. Relationship between hormonal risk factors and the risk of developing breast cancer, and RA, respectively.

Risk factor	Breast cancer	RA
Early age at menarche	↑	↓?
Late age at menopause	↑	↓
Late age at first childbirth	↑	?
High parity	↓	?
Breast-feeding	↓	↓
HRT	↑	×
Oral contraceptives	↑	×

(↑=increased risk, ↓=decreased risk, x=no association, ?=inconclusive)

About 85% of malignant breast tumors are estrogen and/or progesterone receptor positive. Through these receptors, the tumor can bind circulating estrogen from the blood stream, which stimulates growth. To counter this, pharmaceutical agents which block the effect of estrogen on breast tissue, are used. The main agents are Tamoxifen, which is an estrogen receptor modulator, and aromatase inhibitors (AI), which inhibit the production of estrogen. Arthralgia is a very common side effect of AI, and to a lesser extent also of tamoxifen. This has led researchers to investigate whether AI and tamoxifen increases the risk of not just arthralgia, but also of arthritis. Apart from case-reports (142), there are two observational studies published examining the risk of RA following AI and tamoxifen treatment in women with breast cancer (143, 144). These studies have shown that both tamoxifen and AI increase the risk of developing RA. However, they have not been able to consider some potentially important confounders, and they both lacked a proper comparator for the rate of RA.

2 OBJECTIVES

2.1 OVERALL OBJECTIVES

The overarching aim of this thesis was to better understand the association between chronic systemic inflammation, its treatments, and risk of cancer occurrence.

2.2 SPECIFIC AIMS

The specific aims of these this thesis were these:

i) To examine screening patterns and the risk of cervical neoplasia in women with RA treated or not with TNFi.

ii) To examine the risk of cervical neoplasia in women with SLE, overall and with respect to treatment, compared with women from the general population.

iii) To assess the risk of incident malignant neoplasms in patients with RA treated with different bDMARDs.

iv) To examine the relationship between RA and breast cancer, and how it is affected by anti-hormonal therapy for breast cancer.

3 METHODS

3.1.1 Case-control study design

A case-control study is a study in which the study population is sampled on the basis of the outcome, and then previous exposures of interest are compared. Commonly all subjects with an outcome (the cases), but only a subset of all potential controls are sampled. The controls should be sampled from the source population i.e. the same population that gave rise to the cases, and independent of exposure. The level of evidence of a case-control study is often described as lower than that of a cohort study. This is derived from the fact that the sampling of controls can create strong biases, and that if exposure is measured long after it has occurred e.g. in an interview with the subject at disease debut, it would make the study prone to recall bias. Recall bias occurs when cases remember their exposure more (or less) correctly than do controls. A classic example of this is in a study of malformations where mothers that have recently given birth to a baby with a malformation, and mothers that have given birth to a healthy baby, are interviewed about specific exposures during the pregnancy. The mothers that have given birth to a baby with malformations are thought to have gone through all aspects of the pregnancy, during the time that has elapsed between the birth and the interview, looking for a reason for the malformation. Therefore, they are more prone to report exposures resulting in differential misclassification and bias (145). In a case-control study that is conducted using prospectively collected data on exposures, this phenomenon will not occur. The function of the control subjects in a case-control study is to reflect the exposure distribution in the source population that gave rise to the cases. Finding appropriate controls in case-control studies can pose a major obstacle if it is hard to define the source population that gave rise to the cases. Think of a case-control study carried out in a hospital, where all cases of a certain disease during a specific period of time are gathered. The controls should then be sampled from the population that would have been admitted to that hospital, had they gotten the disease. The exact catchment area of a hospital can be hard to pin down, and even if you sample controls from the population of the exact geographical area, they might have been less inclined to seek care than the cases were. If you instead sample controls from patients who have been admitted to the same hospital for a different disease, the exposure may be linked to that disease, or to healthcare seeking behavior. In the case-control study that we conducted in this thesis, **Study IV,** controls were sampled from the entire Swedish population using incidence density based sampling, which should minimize this sort of bias. Incidence density based sampling means that for each new case, controls are sampled from disease-free individuals still at risk at the point in time that the case occurred.

3.1.2 Cohort study design

A cohort study is an intuitive design, in which the study population is sampled on the basis of an exposure, and then followed over a period of time, during which an outcome of interest is recorded. The occurrence of the outcome among the exposed and the unexposed is then compared, typically by calculating an incidence rate. The design is similar to that of an RCT,

with the big difference being that treatment is not randomly assigned, which opens up for bias. A more structured data collection process, and blinding, i.e. that the study participant and/or the researcher do not know which exposure has been allocated, are other important advantages that RCTs often, but not always, have over observational studies. Nevertheless, there are several advantages of cohort studies, e.g. they can potentially include huge study populations, and follow them over a long period of time which increases power and generalizability. Also, contrary to a case-control design, they can study several outcomes in tandem. They are often described as less cost-effective than a case-control study, because in order to study rare outcomes, data must be collected on a large group of subjects, most of which will never develop the outcome. However, this argument does not hold when utilizing registers with data already collected. In this thesis we used a cohort study design in all four studies.

3.1.3 Survival analysis

Survival analysis is a way of estimating the risk of an event by quantifying the time until the occurrence of said event. As the name implies, the event can be death, but these methods can be used to study time until any event of interest (cancer, bankruptcy, lottery win, imprisonment). Perhaps a more intuitive approach would be to compare the proportion of events occurring in the different exposure groups at the end of a study. However, such an approach would not be able to handle inter-individual variations in the person-time contributed. In survival analysis, the subjects can contribute information to the analysis even if information about their survival time is incomplete. If this is the case, the subject contributes information up until the time that they are removed from the risk set, which is called censoring. Censoring occurs for example if the person dies, drops out, is lost to follow up, or if the study ends. In most applications of survival analysis, it is important that the censoring is uninformative, i.e. that it is unrelated to the outcome of the study.

Cox proportional hazards model, or *Cox regression*, is a method in survival analysis that allows for assessing the effect of several variables upon the time it takes for an event to occur. The variables need not be constant but can change over time. The Cox model assumes that the effect of a variable on the hazard is multiplicative. In Cox regression, the baseline hazard is unknown but considered equal for all individuals. As Cox regression is a time to event analysis, the time-scale must be defined. Different time-scales can be chosen depending on what is most appropriate for the study, such as calendar time, follow-up time, or attained age. In our studies we have used both follow-up time and attained age, depending on the study question. If two groups are compared to each other in a clinical study that assesses the outcomes of two drugs, then follow-up time since start of therapy might be the most appropriate time-scale. If instead we want to study the risk of death in women compared to men, then attained age might be the best fit for our model. Additional time-scales can be accounted for in the model. The Cox model assumes that hazards are proportional over time for all included variables. The assumption that hazards are proportional over time does not always hold, and should be tested. There are different ways of assessing if hazards are

proportional over time i.e. visual inspection of the cumulative hazard plots, stratifying the analysis on the time-scale used, or by introducing an interaction term between the independent variable and time.

3.1.4 Selection bias

Selection bias is a situation where a non-causal exposure-outcome relationship has been introduced in the study population that was not present in the source population, due to how the study population was selected or followed up. This means that we are conditioning on a common consequence of the disease and the exposure, as shown in **Figure 3.1,** where there is no direct link between exposure (E), and disease (D), but both cause C, which we are conditioning on (as denoted by the box around C). There are many different situations where this can arise, an intuitive example is the potential bias from studies that included volunteers, where subjects that are at a higher risk (e.g. because of a family history of the disease) might be more, or less, willing to participate. In the context of this thesis, selection bias could arise if the risk of cancer associated with bDMARDs differed between those included in ARTIS, and those that were not.

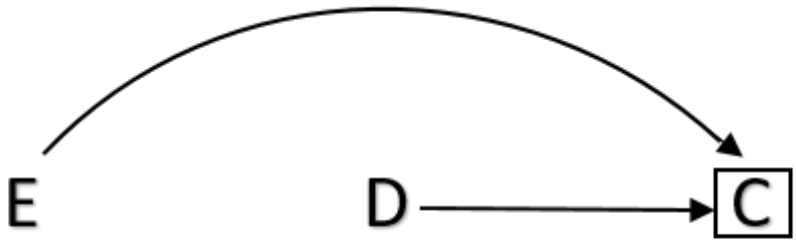

Figure 3.1. Graphical depiction of selection bias. A spurious association between Exposure (E) and disease (D) is introduced by conditioning on a common effect (C).

3.1.5 Confounding

Confounding is a key concept in epidemiology which can bias the estimated effect of the exposure on the outcome. A confounder is a factor that is associated with both the exposure and the outcome, but is not on the casual path between them, or a common effect of them. Another way of describing it is as an open backdoor path between the exposure and the outcome, or a common cause of the exposure and the outcome. **Figure 3.2** shows that there is no direct link between exposure E, and disease D, but both are caused by C, which will produce a spurious association between them, if not accounted for. Confounding can bias the result towards, or away from, the null, and the strength of this bias depends on the strength of the association between the confounder and both exposure and the outcome, as well as the prevalence of the confounder in the population. This means that also an observed null result can be due to confounding, hiding the true effect. Provided that good data are utilized, with

high specificity and sensitivity, it's not hard to handle confounding in a study. Indeed, there are many available methods, such as adjusting in the model, matching, stratification, restriction etc. However, if there is misclassification or missing data, dealing with confounding will be harder, although there are also methods to alleviate this problem (e.g. imputation, quantitative bias analysis). Bias that arises from unknown confounders are perhaps an even larger threat to the validity a study, and there is no way to ascertain that this is not present. An excellent way of dealing with confounding, is by randomizing the exposure among the participants in the study population. Provided that the study population is large enough, this should result in an even distribution of the confounding factors, both known and unknown.

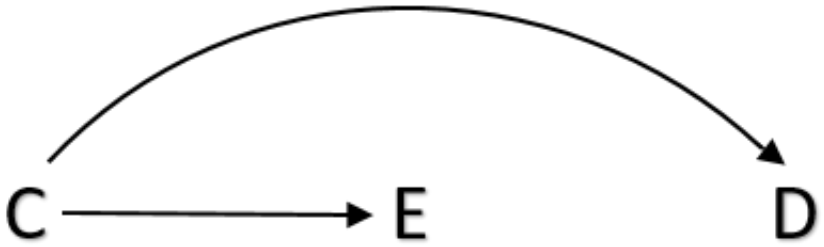

Figure 3.2. Graphical depiction of confounding. A non-causal association between exposure (E) and disease (D) will be the effect of not accounting for the common cause (C).

A certain type of confounding, called *confounding by indication*, or *channeling*, can constitute a major source of bias in observational drug effectiveness or drug safety studies. This arises from the fact the doctors don't randomize patients to different therapies. Instead, they use their clinical expertise, clinical guidelines, past experiences etc. to decide which treatment is the most appropriate for a given patient in a given situation. Perceived, or actual, risks that are associated with specific drugs affect the clinical decision making. In the context of this thesis, this is clearly seen in the low prevalence of previous cancer in TNFi-treated, and the high prevalence of previous cancers in rituximab-treated. This is not unexpected in light of the fact that some treatment guidelines have recommended rituximab, instead of TNFi, in patients with a history of prior malignancy, at least within the first 5 years (146). A variable that is recorded in the data, such as a previous malignancy, can be accounted for in the analysis, e.g. by restricting the analysis to patients with no history of a prior malignancy. However, if a specific therapy is avoided because of subtler reasons, such as a perceived higher risk of a malignancy for the patient, this can constitute a bigger problem. Also, as seen in **Study III**, most patients treated with other bDMARDs had previously been treated with TNFi, and failed. Non-random allocation of treatment is the most important difference between observational studies and RCTs. Actual, or perceived, differences in safety or effectiveness can cause channeling towards, or away from, drugs. Furthermore, the clinician's

treatment decision can be influenced by such factors as, e.g. the cost of the drug, or personal preferences of either the doctor, or the patient. Differences in healthcare organization, drug reimbursement schemes, guidelines and clinical traditions, can further influence channeling and hamper cross-country study comparisons. Whether there is a clear scientific rationale, or not, behind the channeling, it should be addressed in the study design. A recent paper by Frisell et al. tried to map out the patient characteristics of Swedish RA patients initiating bDMARD therapy, and to also predict how these characteristics influenced the risk of outcomes such as malignancy (147). They found that most, but not all, of the difference in predicted risk of malignancies disappeared when age and sex was adjusted for, but that medical history and disease activity also need to be accounted for. In the context of this thesis, confounding by indication was an important issue in **Studies I-III**. Table 1 in **Study III** shows substantial differences between the drug cohorts in terms of e.g. age, sex, education, and medical history (including a previous malignancy).

3.1.6 Measurement error

Measurement error means that the assigned value of a variable differs from the actual value, and is a ubiquitous source of bias in medical studies. First of all, the variable that we have recorded is often not exactly the same as what we are actually interested in, but a proxy. Secondly, it is unlikely that all values are recorded with exact precision. We are concerned with three types of measurement error, that of exposure, outcome, and of confounders. Measurement error can cause differential, or non-differential, misclassification. Non-differential misclassification means that it is independent of other variables in the analysis. Non-differential misclassification of exposure or outcome is often considered less grave than differential, because it will generally bias the estimate towards the null. Differential misclassification means that it is not independent of other variables in the analysis, and can cause bias away from, as well as towards, the null.

In this thesis the outcome is generally cancer, captured through the Cancer Register which has excellent coverage and validity (148). However, the time between inception of cancer to detection can vary greatly, and might be dependent on such factors as screening, frequency of doctors' visits, degree of symptoms etc. Although we can be fairly certain that a subject that has been diagnosed with cancer is a true case, we have no way of ascertaining that a subject is disease free at a given point in time. If, however, cancer detection is dependent on the exposure, then we potentially have an even greater problem, because this will produce a biased estimate of the relative risk between exposed and unexposed. Let's say that our exposure is TNFi, and our outcome is lung cancer. If initiators of methotrexate or TNFi undergo a routine chest x-ray which can potentially detect an underlying lung cancer, and our comparator group doesn't, this can cause differential misclassification of disease.

As for misclassification of exposure, we know that a prescribed drug has been dispensed, but usually we have no way of knowing if the patient has actually taken the drug. Sometimes we have a problem with over-the-counter drugs that haven't been recorded in our registers.

Furthermore, exposure status is often dichotomized which necessitates a cut-off, even though actual exposure might not be so clear cut.

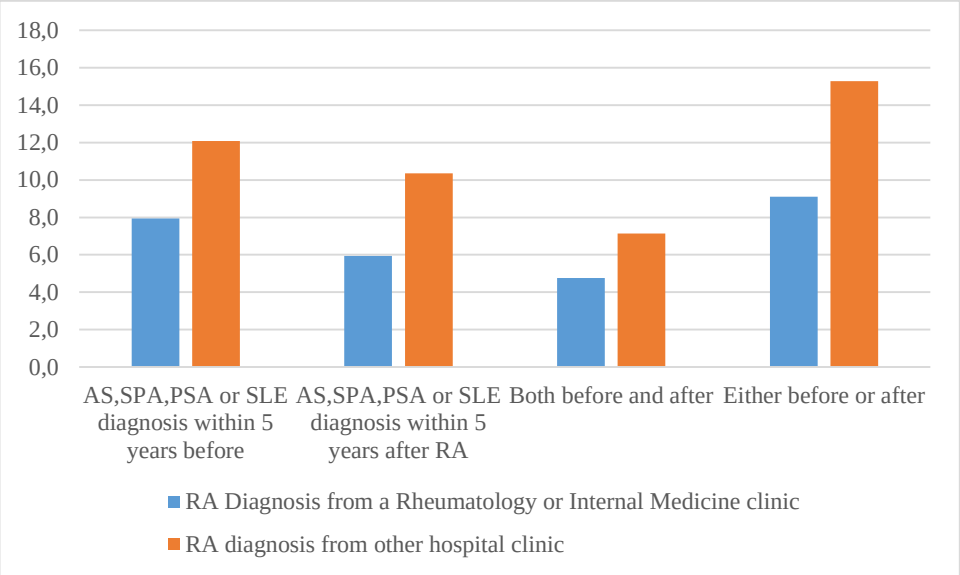

Figure 3.3. Incident RA patients 2006-2010 with ICD-codes for other rheumatic diseases (AS=ankylosing spondylitis, PSA=psoriatic arthritis, SPA=other spondyloarhropathy, or SLE) in the NPR, before and after RA diagnosis, and by clinic.

Rheumatic diseases can present in different ways and what might be an obvious diagnosis at a later point in time might be unclear in the beginning. In this thesis we have used algorithms to identify patients in the patient register based on the type of diagnosis, the number of diagnoses, and where it has been made, but this inevitably leads to a trade-off between sensitivity and specificity, as well as latency period between actual disease onset and start of follow-up. In **Figure 3.3** we see that if we pick a random patient from the NPR with a first RA diagnosis during 2006-2010, there is a 15% chance of that patient having at least one International classification of diseases (ICD) code in the NPR, with a diagnosis of some other rheumatic conditions (ankylosing spondylitis, psoriatic arthritis, other spondyloarhropathy, or SLE) during either the preceding 5 years, or the coming 5 years. We see also that if this diagnosis was made at an internal medicine or rheumatology clinic, the chance is instead 9%. This highlights the importance of proper algorithms being used when adopting a register-based approach for identifying disease.

The algorithm for identifying SLE in the patient register has been reported as highly accurate (positive predictive value of 98%), when validated against clinically confirmed cases (149). The positive predictive value of a similar RA algorithm to the one we used in **Studies I** and **III**, has been reported as 90%, when validated against the 1987-, and 2010, ACR-criteria (12, 150, 151). In **Study IV**, we used the same definition, but also included cases of RA in the Swedish Rheumatology Quality Register (SRQ). Although no guarantee of accuracy, these diagnoses have been assigned by a rheumatologist.

3.1.7 Immortal time bias

Immortal time bias arises when person-time, during which a subject is not at risk for the event is counted in the analysis (145). For example, if the outcome is death, and we require a subject to have two diagnoses of RA to be included, person-time before the date of the second diagnosis should be excluded from the analysis because we have conditioned on the subject being alive up until this point. If we include this time, and compare the survival rates in RA with control subjects that have no such requirement, we will inflate the denominator of RA person-time and overestimate their survival. Although the name "immortal time" implies that death is the outcome, this bias can arise whenever person-time when a subject is not at risk for the event is included, regardless of the outcome. To avoid this error in this thesis, time before all the inclusion have been met has been excluded, or if subjects have been allowed to switch treatment groups, time has been allotted to the appropriate exposure group.

3.1.8 Reverse causation

Reverse causation, refers to a situation where A does not cause B, rather B causes A. Cross-sectional studies, where exposure and outcome are measured at the same point in time, are especially susceptible to this type of bias. In this thesis we used prospectively collected data, which should minimize the risk of this happening. However, it is sometimes hard to determine at which point in time an event occurs. The debut of both rheumatic disease, and cancer can often be insidious, and disease processes will often have started long before it is diagnosed. Even worse, initiating a new treatment might unmask underlying occult disease, such as malignancy. Also, sometimes malignancies present with symptoms that can mimic that of other diseases, including rheumatic disease, so called paraneoplastic phenomena (152). This can result in a subsequent false diagnosis of, e.g. RA, instead of the undiscovered tumor. Reverse causation can be addressed by using a wash-out period, i.e. excluding the time immediately following exposure from the analysis. Other options include performing sensitivity analyses to test the robustness of the findings by moving the index date back and forth, or analyzing the risk stratified by time since start of follow-up.

To address this issue in **Studies I and III**, we performed secondary analyses stratified by time since start of follow-up. The result of these analyses in **Study I** seemed to indicate a trend towards lower risk of cervical dysplasia outcomes, but not of invasive cervical cancer. This could be due to intensified screening associated with start of TNFi, chance finding, or depletion of susceptibles. **In Study III**, there was no clear trend for overall cancer risk when stratifying by time since start of TNFi. Due to the recent introduction of the other bDMARDs, and low power, theses analyses were not performed for other bDMARDs, or other outcomes. In **Study III**, we also performed a sensitivity analysis where a 90-day lag period was added between inclusion and start of follow-up, with similar results compared to the main analysis.

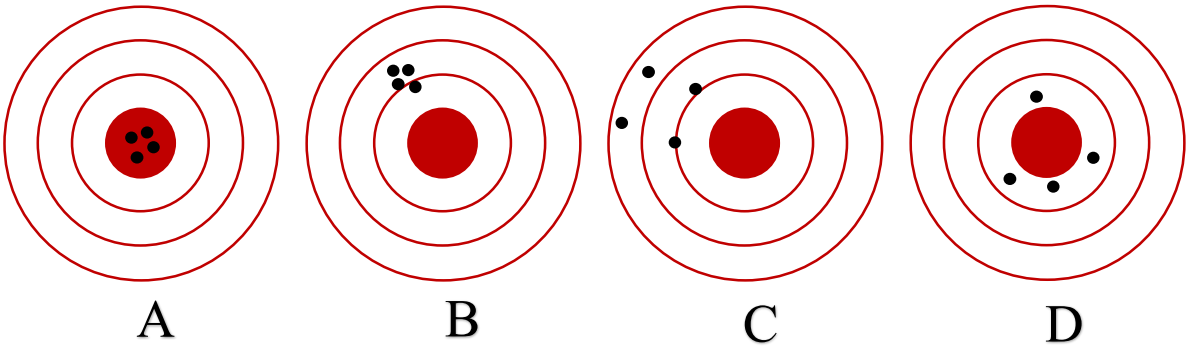

Figure 3.4. Graphical representation of accuracy and precision. A, good accuracy and precision. B, Good precision, bad accuracy. C, Bad accuracy and precision. D Good accuracy, bad precision.

3.1.9 Random error

Confounding, selection bias and measurement error all refer to systematic errors in studies, which are not affected by study size. Random error is the other type of error that can lead to discrepancies between the observed, and the true estimate. Random error decreases with increased study size, which is recognized by lower p-values and narrower CIs. Although important to consider, random error, or the precision of a study, is perhaps sometimes given too much attention. If strong biases in a well-powered study have not been dealt with, we will have a precise estimate of a biased result, such as in **Figure 3.4 (B)**. In this thesis we used a threshold of 0.05 for p-values, and calculated 95% CIs.

3.1.10 External validity

Internal validity refers to in which degree the results of a study is free from bias. External validity refers to the generalizability of the results of the study. If a study is conducted in only men, can we draw inference from that study when it comes to women as well? Whenever the study population is not representative of the target population, this issue might be raised. However, sometimes we do not want the study population to be representative of the target population. In a RCT, rigorous criteria are often applied, as to minimize the noise from factors other than that of the causal effect of the exposure on the outcome. Effect modification, i.e. the effect of X on Y, varies across strata of Z, might be present, but it's not feasible to redo a study under all thinkable conditions, without a biological rationale. There are often trade-offs between internal validity, external validity, and precision. In such cases internal validity should be ranked very high, because if results are not valid, precision and generalizability are meaningless (145).

In this thesis, we have used nationwide registers, with very high coverage of the Swedish RA and SLE populations, which should ensure high generalizability of the results to these respective populations. Nevertheless, there has been some underreporting to the NPR from some private practitioners, which could have led to misclassification of some patients. However, most patients are treated by hospital-based rheumatologists, and some of the missing patients in the NPR have been captured by the SRQ. Also, some patients with mild disease treated in primary care, or in remission, might also be missed.

3.2 DATA SOURCES

This thesis contains four register-based studies conducted on Swedish patients with RA and SLE, respectively. Sweden has a long tradition of maintaining records on its citizens for economic and military purposes, dating back to the 16th century. The 20th century saw the development of many new registers, including healthcare and educational data. Since 1947, all Swedish residents are issued a personal identity number (PIN) which allows for linkage between registers (153). Using algorithms, patients with rheumatic disease can be identified from these registers. These data can then be enriched by information on treatment, comorbidities etc. from other registers, including quality of care registers. This allows for relevant comparisons by treatment and other characteristics within patient populations. Furthermore, by matching these individuals on certain parameters to individuals in the general population, e.g. cancer incidence can be benchmarked against the background risk in the population. Swedish healthcare is population based and tax funded and reporting to the healthcare registers is mandatory for clinicians. This ensures a high coverage and minimizes the risk of selection bias, thus providing a (near-) perfect setting for register-based medical studies.

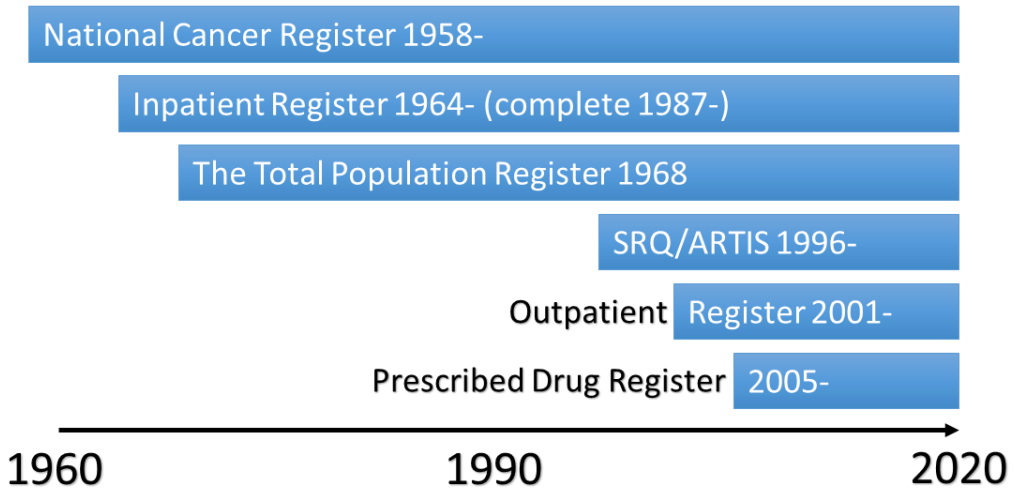

Figure 3.5. Timeline depicting the inception of Swedish registers utilized in this thesis

3.2.1 The Swedish Rheumatology Quality Register

The SRQ was started in the late 1990's to follow patients with RA. Since then, it has expanded to include other rheumatic diagnoses. The register serves as an integrated support tool in clinical decision making. At each visit, the clinician enters data on disease activity, disability and treatment, which can thus be followed longitudinally. ARTIS is a subset of the SRQ for patients treated with bDMARDs. ARTIS has an estimated coverage of 95% of bDMARD treated patients in Sweden, and validation against the PDR indicate a high degree of coherence (154). This register was used to identify bDMARD treatments in **Study I** and **III**, and incident RA patients in **Study IV.**

Table 3.1. The main data sources that were used in the studies included in this thesis, and what information was used from them		
Data source	**Identification of subjects**	**Data used**
The Swedish Rheumatology Quality Register	Patients with RA	Health assessment questionnaire, Disease activity score of 28 joints, treatment information (1999-)
National Patient Register	Patients with main or contributory diagnosis for Rheumatoid arthritis and Systemic lupus erythematosus	Health care use and comorbidities (not primary care; inpatient: 1971-; outpatient: 2001-)
Cause of Death Register	-	Deaths (1956-)
Prescribed Drug Register	-	Dispensed drug prescriptions (not in-hospital drug use; July 2005 -)
Cancer Register	-	Information on incident cancers (date, ICD-code, TNM-stage, 1958-)
Cervical Screening Registry	-	Cytology and histopathology testing
Register of the Total Population	Sampling of comparators/controls	Birth, death, civil status, country of birth, migration (1968-)
Longitudinal integrated database for health insurance and labor market studies	-	Level of education (1990-). Sick-leave and disability pension (1994-)
Multi-generation register	-	Children, family history of cancer (together with the cancer register)

3.2.2 The National Patient Register

The National Patient Register (NPR) is administered by the National Board of Health and Welfare and was founded in 1964. It contains data on every discharge from inpatient care since 1987, and since 2001 visits in non-primary outpatient care are also included. Each discharge or visit is ICD-coded, with clinic, date, and main- and contributory diagnoses specified (155). The NPR was used in **Studies I-IV** to identify RA and SLE patients, as well as comorbid conditions.

3.2.3 The Swedish Cancer Register

The Swedish Cancer Register was started in 1958 and is administered by the National Board of Health and welfare. Reporting of incident cancers is mandatory for all health care providers and the coverage is estimated at >95% (148). Both the clinician and the

pathologist/cytologist report to the register. Apart from administrative data (PIN, hospital), medical data on site of tumor (ICD), basis (clinical or histopathological) and date of diagnosis are recorded in the regsiter. Also, since 2002, histological type is coded according to TNM Classification of Malignant Tumours (TNM) or The International Federation of Gynecology and Obstetrics classification. The Cancer Register was used in **Studies I-IV** to identify incident and previous cancers.

3.2.4 The Prescribed Drug Register

The Prescribed Drug Register (PDR) was set up in 2005 and gathers data on prescribed drugs in Sweden (156). Each dispensed drug is listed according to the Anatomical Therapeutic Chemical Classification System, along with dose, quantity, date, and customer PIN. It does not capture over the counter drugs. Hospital-administered drugs, including intravenous bDMARDs, are only partially captured (e.g. infliximab and rituximab). The PDR was used in **Studies I-IV** to identify dispensed prescriptions.

3.2.5 The Total Population Register

The Total Population Register started in 1968 and is administered by the Swedish Tax Agency. It contains data on all long-term Swedish residents. Each person is listed by PIN, sex, name, birth data (where and when), address, emi- and immigration, income and citizenship (157). The register also contains the Multi-generation register, through which data on parents, children, and siblings can be identified for Swedish residents 1961-, and people born in Sweden 1932 or later. Coverage is high for persons born in Sweden 1968 or later, but lower for immigrants, adopted children, and older cohorts. The register also includes the longitudinal integrated database for health insurance and labor market studies (LISA) which integrates existing data from the labour market, educational and social sectors. Information from the Total Population Register on education, birth, migration, education, sick-leave and disability pension as well as family history, was used in **Studies I-IV** of this thesis**.**

3.2.6 The National Cervical Screening Registry

Female residents in Sweden, aged 23-64, are invited to partake in cervical screening. The National Cervical Screening Registry (NKCx) gathers data on screening invites and all cervical screenings (and ensuing cytology and histology tests) in Sweden, both opportunistic and pre-planned. All laboratories have reported cytological results since 1997, and histological results since 1998 (158). The coverage for cervical cytology and histology tests has been estimated at >90%. In 2012, an estimated 64% of invited women (aged 23-60) had a cervical smear recorded within 1 year of the invitation. The same year, 69% of registered pap-smears were classified as pre-planned, as opposed to opportunistic. Data from the NKCx was used to identify screening appointments, and cytology/histopathology for premalignant lesions in **Studies I-II**.

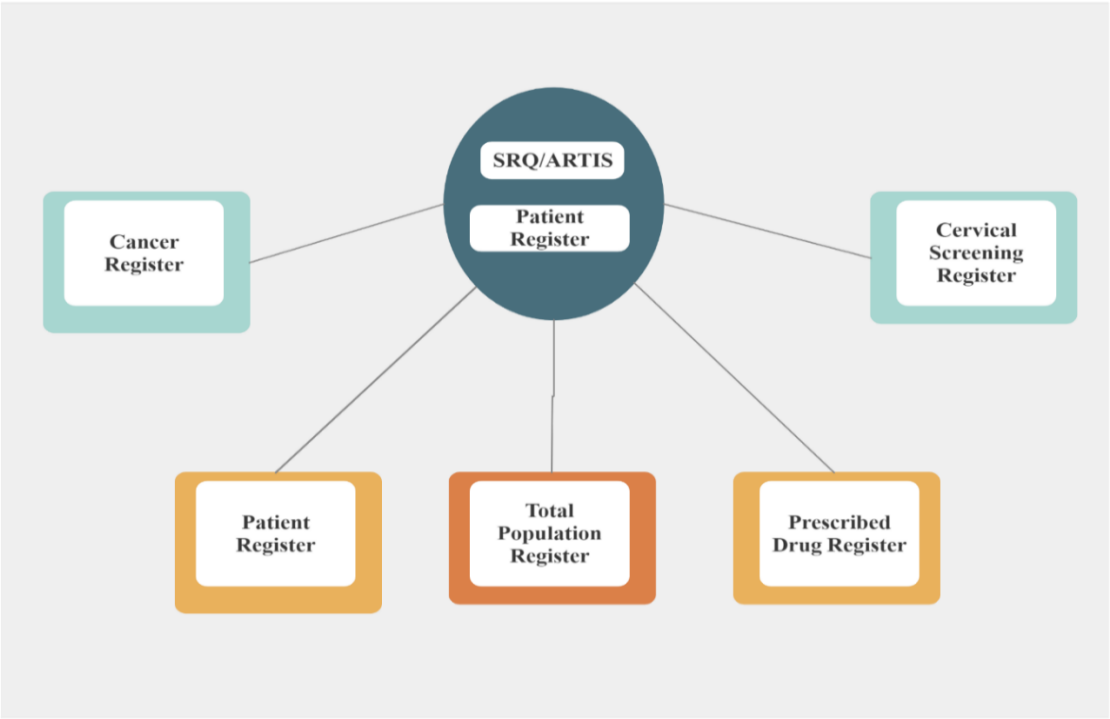

Figure 3.6. Illustration of register linkages. Patients are identified in SRQ/ARTIS and/or the Patient Register, and these data are enriched by linkages to registers with data on comorbidities, drug dispensings, socioeconomy and demography.

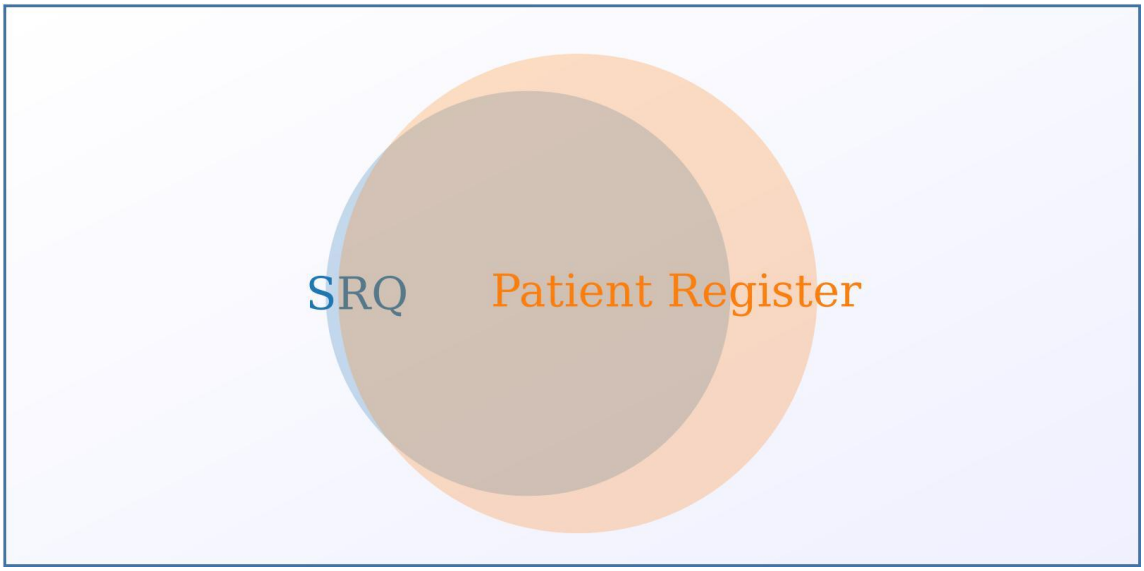

Figure 3.7. Overlap between prevalent patients 2006-2016 registered as RA patients in SRQ, and identified in the Patient Register using an algorithm with a requirement of at least 2 visits, 1 of which had to have been at a Rheumatology or Internal Medicine clinic.

3.3 ETHICAL CONSIDERATIONS

The studies presented in this thesis are all register-based studies. All subjects are anonymized. Data are only kept on secure servers with restricted access. The Regional Ethical Review Board in Stockholm has reviewed and approved these studies.

A lack of informed consent is problematic and at least seemingly at odds with Helsinki declaration. However, according to Swedish law, research may be carried out without informed consent if it can be assumed that it may provide knowledge unattainable elsewise, and it may be of direct benefit to the subject or patients with the same condition, provided that it does not cause significant harm to the study subject. The study must be reviewed in advance by an ethical review board.

The studies presented in this thesis deal with cancer as a comorbid condition to rheumatic disease. These conditions cause physical and mental harm to patients and their families, and are often fatal. The studies we are conducting can hopefully contribute knowledge to the field and are of direct clinical relevance. An increased understanding of the risks facing these patients may help us tailor their treatments properly so as to alleviate, or even preempt disease. Our belief, and our hope, is that the benefits of having conducted these studies outweigh the potential harm caused by them.

4 STUDY DESIGN AND RESULTS

4.1 OVERVIEW

All four studies were completely register-based. Different registers were linked together to identify the study populations and data on their exposures, outcomes, and potential confounders. Also, all four studies were cohort studies, although in **Study IV** a case-control design was also adopted. All studies were performed using SAS statistical software (version 9.4; SAS Institute Inc)

In **Study I** and **III**, RA patients (incident or prevalent) and their respective bDMARD therapies were identified through ARTIS. Thus we chose to rely on the RA diagnosis in ARTIS, and did not incorporate information from the NPR. In both of these studies biologics-naïve comparator cohorts were set up. Although the SRQ contains a substantial proportion of biologics-naïve RA patients in Sweden, coverage is not complete and causes related to inclusion in the SRQ could bias the relationship between RA and adverse outcomes, including cancer. Therefore, when setting up biologics-naïve RA comparator cohorts we used algorithms to identify them in the outpatient subset of the NPR instead. We required two or more visits with an RA ICD-code as the main or contributory diagnosis. At least one visit had to have been at an internal medicine or rheumatology clinic. By linking these patients to the PDR, active comparator csDMARD-treated cohorts could be set up. In **Study IV**, new-onset RA patients were identified by combining information from the SRQ and the NPR. Patients were required to have either 1) two visits in the outpatient subset of the NPR with an RA diagnosis (main or contributory), and at least one visit in a rheumatology or internal medicine clinic, or 2) an RA diagnosis in the SRQ. No more than 18-months were allowed to have passed between a first arthritis diagnosis, or the date of disease debut recorded in the SRQ, whichever occurred first, and fulfillment of the diagnosis defining criteria listed in 1) or 2). In **Study II,** SLE patients were identified through the NPR, using algorithms similar to those in **Study I** and **III.** We required two visits in either in- or outpatient care in the NPR, with an ICD-coded SLE diagnosis (excluding drug-induced Lupus). Also, at least one diagnosis had to have been from a department or specialist typically known to diagnose, treat or manage SLE (rheumatology, dermatology, nephrology, internal medicine and pediatrics).

In all four studies, general population comparator cohorts were set up by linkage to the Total Population Register, matched 1:5, or 1:10, on vital status, sex, year of birth and place of residence.

Table 4.1. Overview of the four studies				
	Study I	Study II	Study III	Study IV
Short Title	RA, TNFi and the risk of cervical neoplasia	Cervical neoplasia in SLE	Immunomodulators and Risk of Malignant Neoplasms	Breast cancer and RA
Design	Cohort	Cohort	Cohort	Cohort and Case-control
Disease	RA	SLE	RA	RA
Comparison	TNFi vs. csDMARD; csDMARD vs. General population	SLE vs. general population; antimalarials vs. immuno-suppressants	TNFi, rituximab, abatacept, tocilizumab vs. csDMARD	Incident RA vs. General population
Data source	Swedish registers	Swedish registers	Swedish registers	Swedish registers
Study period	1999-2012	2006-2012	2006-2015	2006-2016
Outcomes	Cytology screening with normal outcome, LSIL, HSIL, invasive cervical cancer	Overall cervical neoplasia, LSIL, HSIL, invasive cervical cancer	Overall cancer, solid malignancy, hematologic malignancy, squamous cell skin cancer, melanoma	Breast cancer in patients with RA, RA in patients with breast cancer, with or without anti-hormonal treatment

4.2 STUDY I

Study I was a cohort study in which cervical screening and the risk of cervical neoplasia in women with RA was examined 1999-2012.

Exposure

We defined three exposure groups, 1) biologics-naïve women with RA starting a TNFi as the first ever biologic, 2) biologics-naive women with RA in general, 3) general population referents.

1) In ARTIS, we identified all RA patients who initiated TNFi therapy as their first ever bDMARD. Start of follow-up was set to the date of TNFi therapy inititation. In the main analysis, a once exposed always exposed approach was adopted.
2) In the outpatient subset of NPR, we identified all women with two or more visits with an RA ICD-code as the main or contributory diagnosis. At least one visit had to have been at an internal medicine or rheumatology clinic. Patients with a prior diagnosis of juvenile idiopathic arthritis, ankylosing spondylitits, SLE or psoriatric arthritis were excluded. Start of follow-up was defined as the first date when all the inclusion

criteria were fulfilled. Patients were censored at start of first bDMARD, and if that was a TNFi, they were allowed to switch cohorts to the TNFi cohort.

3) By linking the biologics-naïve RA cohort to the Population Register, a general population comparator cohort was set up. For each RA patient, 10 randomly selected referents were identified, matched on year of birth, sex, and county of residence. Start of follow-up was set to that of their respective biologics-naïve patient with RA.

Outcomes

Four different outcomes were defined using data from the NKCx and the Cancer Register.

1) A first cytology screening, either pre-planned or oppurtunistic, with a normal outcome during follow-up
2) First LSIL in individuals with no prior cervical dysplasia or invasive cervical cancer, before (excluded). Subjects were censored on HSIL or invasive cervical cancer during follow-up.
3) First HSIL during follow-up in individuals with no prior HSIL or invasive cervical cancer (excluded). Subjects were censored on invasive cervical cancer during follow-up.
4) First invasive cervical cancer during follow-up in individuals with no history of invasive cervical cancer at start of follow-up.

Covariates and statistics

End of follow-up was defined as first of 31 December 2012, death, emigration, a total hysterectomy, date of any solid organ transplantation and occurrence of the outcome under study. We computed the crude incidence, and performed Cox regression analyses. Covariates that were considered in our models were age, year of birth, educational level, marital status, previous screening, healthcare utilization and comorbidities. In a subset of the study population, we had access to data on parity and family history of cancer, and therefore the effect of these potential confounders were assessed separately. Attained age was used as the time-scale in Cox regression analyses, but alternative time-scales were also tested (follow-up time, calendar time).

In addition to the main analysis, several sensitivity analyses were performed. In order to have an active comparator, and a more contemporary set of patients treated with TNFi, we restricted the study period to 2006-2012, and added a requirement of csDMARD treatment for the biologics naïve RA cohort. In the same sensitivity analysis, we also assessed the risk for new-users of TNFi 2006-2012. Also, the effect of two alternative exposure time-windows was tested instead of *ever-since first exposure*. *On-drug* in which TNFi-treated patients were censored after discontinuation of the specific TNFi-agent (+90 days), and *on-class,* in which TNFi-treated patients were kept in the risk set upon switching to another TNFi-agent, but censored on TNFi discontinuation (+90 days) (Figure 4.1).

Main results of study I

We included 9629 TNFi initiators, 34,984 biologics-naive women with RA and 300,331 general population comparators in our analyses. The TNFi cohort was younger, and had achieved a higher level of education, compared with the other cohorts. At baseline, a majority of TNFi initiators (71%) were treated with at least one concomitant csDMARD, and had a disease duration of 8.2 years.

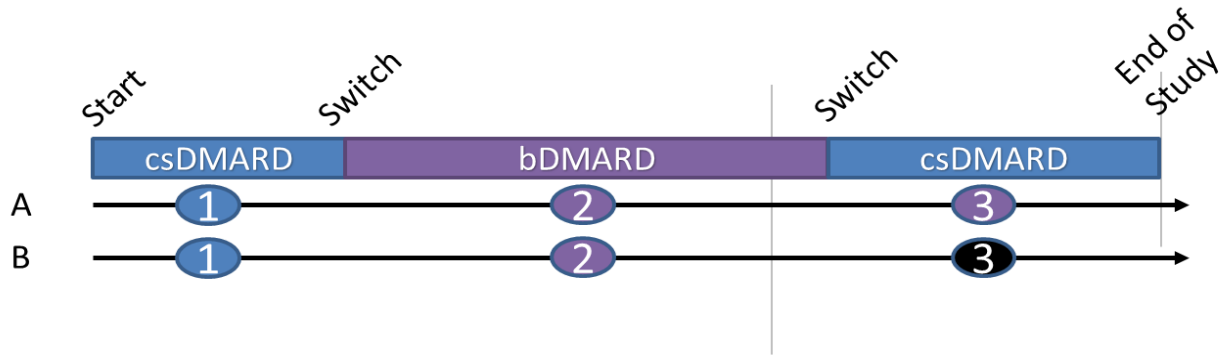

Figure 4.1. Representation of alternative exposure windows. Patients are considered bio-naïve until start of first bDMARD, at which point they switch cohorts. In Scenario A, we use an "ever exposed" approach when considering bDMARD treatment, event 1 is thus counted towards the csDMARD-cohort, and events 2-3 are counted towards the bDMARD-cohort, even though event 3 occurred after bDMARD treatment cessation. In scenario B, using an "on drug" approach when considering bDMARD treatment, event 3 is not counted in the analysis because it occurred after termination of treatment.

Comparing biologics-naive RA with the matched general population comparators, we noted no differences in age-adjusted Cox regression for time to first screening with normal result, with a hazard ratio (HR) of 1.01 (95%CI 0.99-1.03) (Table 4.2). Cox regression adjusted for demographic factors, socioeconomic factors, previous screening and comorbidities, revealed a slightly higher HR for biologics-naïve RA, HR=1.08 (95%CI 1.06-1.10). The risk of both LSIL, and HSIL, was increased among biologics-naïve RA, with fully adjusted HRs of 1.53 (1.23-1.89), and 1.39 (1.16-1.66), respectively. Both crude and adjusted rates of invasive cervical cancer were similar between biologics-naïve RA and the general population compators.

In the TNFi cohort, the adjusted rate of cervical screening was similar to that of biologics-naïve RA, HR=1.01 (95%CI 0.98-1.05) (Table 4.2). The risk of LSIL was not statistically significantly increased, HR=1.23 (95%CI 0.87-1.74). However, the fully adjusted rates of both HSIL, HR=1.36 (95%CI 1.01-1.82) and invasive cervical cancer HR=2.10 (95%CI 1.04-4.23), were higher in TNFi initiators.

For LSIL and HSIL, comparing TNFi initiators to biologs-naïve, there were no obvious differences in HR across follow-up (if anything a downward trend in HRs). For invasive cervical cancer, small numbers limited comparisons.

Several sensitivity analyses were conducted in which we tried to map out the effect of different exposure definitions ("on drug" instead of "ever treated"), past cervical screening

history, family history of cervical cancer, parity et.c, with results which were mostly in accordance with the main analyses. Restriced to subjects with a normal cervical screening as the most recent result, there was a high risk of invasive cervical cancer among TNFi inititators compared to biologics-naïve RA (HR=3.77, 95%, CI 1.35-10.48). On the other hand, we found only one case of invasive cervical cancer during 18,000 person-years, in an analysis restricted to more recent initiators of TNFi (2006-2012).

Table 4.2. Number of persons and events, crude incidence, and hazard ratios for the different cervical outcomes under study.

Outcome definition	Cohort	Number of events	Crude incidence per 100,000 pys	Adjusted* HR	Adjusted* HR
First screening with normal result	TNFi	4362	14 599	1.01 (0.98-1.05)	
	Bio-naïve RA	10 958	9224	REF	1.08 (1.06-1.10)
	Gen pop	114 943	9556		REF
LSIL	TNFi	52	95	1.23 (0.87-1.74)	
	Bio-naïve RA	99	57	REF	1.53 (1.23-1.89)
	Gen pop	852	45		REF
HSIL	TNFi	75	136	1.36 (1.01-1.82)	
	Bio-naïve RA	137	79	REF	1.39 (1.16-1.66)
	Gen pop	1332	70		REF
Invasive cervical cancer, overall	TNFi	14	24	2.10 (1.04-4.23)	
	Bio-naïve RA	25	14	REF	1.09 (0.71-1.65)
	Gen pop	275	14		REF

*= Stratified on decade of birth and adjusted for educational level, number of cervical screens past five years, co-morbidities, marital status and total days spent in hospital during last 5 yrs, also implicitly adjusted for age since age was used as the model's time scale

4.3 STUDY II

Study II was a cohort study in which the risk of cervical neoplasia, overall and with respect to treatment, was examined 2006-2012, and compared to that of the general population.

Exposure

Female patients with SLE during 2001-2012 were identified in the NPR. By linking this cohort to the Total Population Register, a cohort of general population comparators, matched 1:5 on sex, year of birth and, county of residence, was set up. Also two sub-cohorts of SLE patients were defined based on treatment with antimalarials or other immunosuppressants. The immunosuppressants cohort consisted of SLE patients with at least one filled prescription of mycophenolate mofetil, azathioprine, cyclophosphamide, ciclosporin, methotrexate, or rituximab. Person-time in this sub-cohort was classified as once exposed, always exposed. The antimalarials sub-cohort consisted of SLE patients who had filled at least one prescription of hydroxychloroquine or chloroquine phosphate. Patients in the antimalarials sub-cohort with previous exposure to immunosuppressants were excluded. Patients in the

antimalarials sub-cohort were censored at first filling of an immunosuppressant prescription, with subsequent switching of sub-cohorts.

Outcomes

Outcomes were identified using data from both the NKCx and the Cancer Register. The main outcome was a composite outcome defined as a first LSIL, HSIL, or invasive cervical cancer. As secondary outcomes, the main outcome was split into three separate outcomes:

1. A first ever LSIL, in women with no history of cervical dysplasia or invasive cervical cancer before start of follow-up, and no HSIL or invasive cervical cancer during follow-up.
2. A first ever HSIL, in women with no history of HSIL or invasive cervical cancer before start of follow-up, and no invasive cervical cancer during follow-up
3. A first ever invasive cervical cancer

Covariates and statistics

End of follow-up was defined as first of 31 December 2012, death, emigration, a total hysterectomy, date of any solid organ transplantation and occurrence of the outcome under study. In all analyses, the full SLE cohort was compared to the general population comparators, and the treatment-defined sub-cohorts were compared to each other. Participation in cervical screening was analyzed using t-tests and Cox regression. For the primary and secondary outcomes, we compared the crude incidence and performed Cox regression analysis with attained age as the time-scale, and adjusted for start year, level of education, healthcare utilization, number of children, marital status, family history of cervical cancer and prior cervical screening. Also, in head-to-head analyses of the two sub-cohorts, we adjusted for prior oral corticosteroids and oral contraceptives at baseline. To investigate effect modification by age and thus any non-proportionality over the time scale used, we plotted hazard functions, introduced an interaction term between the exposure and the time scale, and stratified analyses on three age bands (23-44, 45-64 and 65+ years old).

Several sensitivity analyses were performed. To account for disease duration, we examined risks among women who were diagnosed with SLE for the first time in the NPR <2 years prior to the start of follow-up. Also, we analyzed models adjusted for use of oral corticosteroids during follow-up. Lastly, in another sensitivity analysis, patients with at least one dispensing of leflunomide, tacrolimus or sirolimus were also included in the immunosuppressants sub-cohort.

Main results of study II

The full SLE cohort consisted of 4976 women with SLE, of whom 1942 fulfilled the entry criteria for the antimalarials sub-cohort, and 2175 for the immunosuppressants sub-cohort

(including 473 subjects who switched cohorts and contributed person-time to both) (Table 4.3). Median age at entry was 51 in the full SLE cohort, 49 in the antimalarials cohort, and 46 in the immunosuppressants cohort. At entry, time since first SLE diagnosis in the outpatient register was shorter in the antimalarials cohort (median 2.5 years), than in the immunosuppressants cohort (median 3.7 years). Comorbidities were more frequent and healthcare utilization was higher in the immunosuppressants cohort, than in the antimalarials cohort. We noted numerical differences in cervical screening during follow up, but cox regression analyses of time to first screen, taking age and follow-up time into account, revealed no statistically significant differences across any of the SLE cohorts, or vs the general population.

Table 4.3. Risk of cervical dysplasia and invasive cervical cancer among the cohorts of SLE patients and matched subjects.

	Number of patients at risk	Number of events	Total follow-up, years	Crude incidence per 100,000 person-years	Fully adjusted HR (95% CI)[b]
Composite outcome of cervical dysplasia and cancer					
Full SLE	4550	121	23136	523	2.12 (1.65-2.71)
General population	28113	336	155543	216	REF
Immunosuppressants[a]	1981	73	9002	811	1.83 (1.15-2.91)
Antimalarials[a]	1783	26	6564	396	REF
First ever LSIL					
Full SLE	4550	53	23136	229	2.33 (1.58-3.44)
General population	28113	115	155543	74	REF
Immunosuppressants[a]	1981	30	9002	333	2.33 (1.08-5.02)
Antimalarials[a]	1783	9	6564	137	REF
First ever HSIL					
Full SLE	4619	75	23589	318	1.95 (1.43-2.65)
General population	28299	232	156738	148	REF
Immunosuppressants[a]	2022	43	9229	466	1.44 (0.82-2.54)
Antimalarials[a]	1812	19	6687	284	REF
First ever Invasive cervical cancer					
Full SLE	4976	5	25666	19	1.64 (0.54-5.02)
General population	29703	17	165412	10	REF
Immunosuppressants[a]	2175	5	10011	50	NA[c]
Antimalarials[a]	1942	0	7268	0	REF

[a] Subsets of "Full SLE". Data on exposure from the Prescribed Drug Register 2006-

[b] Adjusted for level of education, healthcare utilization, number of children, marital status, family history of cervical cancer, prior cervical screening, and start year. Models comparing SLE immunosuppressants vs. SLE antimalarials were additionally adjusted for use of oral contraceptives and oral steroids at baseline.

[c] Hazard ratios were not calculated if there were less than 5 events in the smallest cell

Comparing the full SLE cohort to the general population comparators, the risk of a cervical neoplasia was higher, with a fully adjusted HR= 2.12 (95%CI 1.65-2.71) (Table 4.3). Secondary outcomes revealed increased risks of both LSIL and HSIL, but not of invasive cervical cancer (HR=1.64 (95%CI 0.54-5.02). When analyzing the outcomes according to drug exposures, we noted an almost doubled risk of a first neoplasia among immunosuppressants- treated, compared with antimalarials- treated (HR=1.83 95%CI 1.15-2.91). Furthermore, all five cases of invasive cervical cancer were in the immunosuppressants cohort.

Several sensitivity analyses were performed, stratifying the analyses on different age-bands, restricting to more recent SLE, adjusting for use of oral corticosteroids during follow-up etc. but these did not alter the interpretation of the main findings.

4.4 STUDY III

Study III was a cohort study in which we assessed the risk of incident malignancies 2006-2015 in patients with RA treated with different bDMARDS.

Exposure

In ARTIS, we identified RA patients who during our study period, initiated treatment with a first TNFi, or a second TNFi, respectively, as well as three other bDMARD cohorts consisting of RA patients initiating a first tocilizumab-, abatacept-, or rituximab treatment. In addition, we defined a biologics-naïve comparator cohort consisting of RA patients treated with at least 1 csDMARD (methotrexate, leflunomide, azathioprine, cyclosporine, antimalarials, sulfasalazine, or gold). Through linkage of the bDMARD-treated cohorts to the Total Population Register, a general population comparator cohort was assembled.

Outcomes

We defined and assessed 5 separate outcomes: 1) a first invasive solid or hematologic malignant neoplasm, excluding NMSC, 2) a first invasive solid malignant neoplasm, excluding NMSC, 3) a first invasive hematologic malignant neoplasm, 4) a first invasive squamous cell skin cancer, 5) and a first invasive melanoma.

Covariates and statistics

End of follow-up was defined as first of 31 December 2015, death, emigration, date of any solid organ transplantation and occurrence of the outcome under study. In the main analysis the five bDMARD cohorts were assessed together with the csDMARD cohort as the reference. Relative risks were estimated using Cox regression, with follow-up time as the time-scale. In the full models, we adjusted for sex, start year, educational level, four comorbidities (ischemic heart disease; chronic obstructive pulmonary disease, diabetes mellitus, and previous knee/ankle/hip/shoulder-surgery), and healthcare utilization (number of hospitalizations and days spent in in-hospital care), sick-leave, disability pension, and baseline use of 1) oral prednisolone, 2) NSAIDs, and 3) and total number of prescription

drugs. Furthermore, because of missing data for the bDMARD-naïve patients, only analyses between different bDMARD cohorts were adjusted for HAQ, DAS28-CRP, erythrocyte sedimentation rate, CRP, and RA disease duration. Analyses between different bDMARD cohorts were also adjusted for prior bDMARD therapy.

In addition to the main analyses, sensitivity analyses with alternative definitions of the bDMARD-naïve cohort were performed, one with no requirement of csDMARD-treatment, and one in which csDMARD-patients were followed from the date of switching or addition of a new csDMARD agent. To account for potential detection bias and reverse causality, another sensitivity analysis in which we added a 3-month lag period between start of bDMARD therapy, and start of follow-up, was performed.

Main results of study III

We identified a total of 15,129 initiations of TNFi as the first or second bDMARD, 1798 of tocilizumab, 2021 of abatacept, and 3586 of rituximab. Also, a comparator cohort of 46,610 RA patients treated with csDMARDs were identified. There were some differences in characteristics at entry between the cohorts. For example, rituximab initiators were more often seropositive, and older, than other bDMARD initiators. Mean follow-up was shorter in the non-TNFi cohorts compared to the TNFi cohorts, owing to their more recent market introduction, and disease duration was longer.

Table 4.4. Hazard ratios and 95% CI for the different outcomes under study in Swedish cohorts of patients with RA initiating tocilizumab, abatacept, or rituximab, ever treated analysis with incidences compared to those initiating TNFi therapy.

Outcome definition, type of invasive malignancy	Tocilizumab	Abatacept	Rituximab	TNFi
Solid/hematologic (no NMSC)	1.12 (0.81-1.54)	1.10 (0.82-1.48)	1.06 (0.86-1.30)	REF
Solid (no NMSC)	1.14 (0.81-1.59)	1.04 (0.76-1.42)	1.05 (0.84-1.31)	REF
Hematologic		1.82 (0.81-4.05)	1.12 (0.62-2.04)	REF
Squamous cell skin cancer	1.04 (0.39-2.80)	2.12 (1.14-3.95)	1.05 (0.62-1.77)	REF
Melanoma		2.39 (0.90-6.33)	1.07 (0.47-2.45)	REF

Adjusted for age, sex and stratified on start year, comorbidities and educational level, rheumatoid factor, number of hospitalizations and days spent in inpatient care (1987-), use of prednisolone at baseline, use of NSAID at baseline, number of prescription drugs at baseline, and sick leave and disability (yes/no) year before cohort entry, disease duration, DAS28-CRP, CRP, erythrocyte sedimentation rate, HAQ, and previous bDMARD therapy (yes/no).

For the main outcome, a first invasive solid or hematologic malignant neoplasm excluding NMSC, we found no statistically significant risk difference between any of the bDMARD cohorts and the csDMARD cohort. The same was true for a first invasive solid malignant neoplasm excluding NMSC, a first invasive hematological malignancy, and a first invasive melanoma. For a first invasive squamous cell skin cancer, we found an increased risk among abatacept initiators, which was attenuated when adjusting for potential confounders, (fully adjusted HR=2.15, 95%CI 1.31-3.52).

Alternative definitions of the bDMARD-naïve RA comparator cohort were investigated in a sensitivity analysis, with similar results as the main analysis. Also, adding a lag period between the start of treatment and start of follow-up, did not significantly alter the results.

As a benchmark for the cancer rates in our RA cohorts, we calculated HRs comparing the csDMARD-treated cohort to the general population comparator cohort. The risk for the combined outcome of a first invasive solid or hematologic malignant neoplasm, excluding NMSC, was 1.11 (csDMARD vs. general population, 95% CI, 1.01-1.22), adjusted for age, sex, and start year. There was also an increased risk for a first invasive hematologic malignant neoplasm (HR, 1.56; 95%CI, 1.13-2.16), and a first invasive squamous cell skin cancer (HR,1.48; 95% CI, 1.03-2.13).

4.5 STUDY IV

Study IV was a combined cohort, and case-control study in which we assessed the risk of breast cancer in incident RA patients 2006-2016 (cohort), the risk of RA in women with a history of breast cancer (case-control), and the risk of RA in women with a history of breast cancer treated with anti-hormonal therapy (case-control).

Exposure and outcomes

In the analysis of breast cancer in patients with RA, we compared the incidence of breast cancer, invasive or in situ, in new-onset RA 2006-2016 to that of matched general population comparators.

In the analysis of risk of RA in women with a history of breast cancer, we compared breast cancer exposure (invasive or in situ, 1958-) among incident RA cases, to that of matched controls from the general population. We then compared the risk of RA, between women with breast cancer that were treated with tamoxifen, or AI, respectively, to that of women with breast cancer that were not treated with these agents, and women without breast cancer.

Covariates and statistics

We assessed the crude incidence of breast cancer and performed Cox regression analysis, gradually adjusted for age, calendar year, educational level, country of birth, number of live births and age at first full-term pregnancy, previous invasive cancer, family history in a first-degree relative of breast cancer or ovarian cancer, use of oral contraceptives and intrauterine devices, and HRT. Age 50 was used as a proxy for menopausal status. End of follow-up was

defined as December 31st 2016, death, emigration, or breast cancer, whichever occurred first. The risk of breast cancer was assessed overall, stratified by time since start of follow-up, by RA serostatus, and age at RA diagnosis. Furthermore, relative risks were assessed according to menopausal status, and TNM cancer stage.

To assess the risk of RA in women with a history of breast cancer, we used a case-control design. Odds ratios (ORs) were computed using conditional logistic regression adjusted for the matching factors, country of birth, educational level, age at first live birth, number of live-born children, and family history of breast- or ovarian cancer. The risk was assessed overall, by time between the breast cancer and RA, by menopausal status, TNM stage, age at RA diagnosis, and RA subtype.

Finally, to assess the risk of RA associated with anti-hormonal breast cancer treatment (2005-2016) we again used conditional logistic regression. We categorized subjects as tamoxifen only-treated, AI only-treated, both tamoxifen- and AI-treated, never tamoxifen- or AI-treated, and no breast cancer prior to index date. We also analyzed the risk with cumulative exposure of anti-hormonal treatment. To deal with detection bias, a sensitivity analysis in which we excluded subjects with less than one year between the breast cancer diagnosis and index date was performed.

Main results of study IV

We identified 15,921 incident patients with RA, who were matched on age, sex, and place of residence, with 79,441 randomly selected subjects from the general population. In both groups, mean age at baseline was 59 years, and 10% had a family history of breast- or ovarian cancer. Except for a somewhat lower level of education among RA patients (more than 12 years of education, RA vs population referents, 15% vs. 19%), and a higher prevalence of family history of RA (10% vs 4%, RA vs population referents), characteristics at baseline were similar between the groups.

During follow-up, we identified 190 cases of breast cancer among RA patients, and 1191 cases among population comparators, fully adjusted HR=0.80 (95%CI 0.68-0.93). The fully adjusted model included age, calendar year, country of birth, educational level, HRT, oral contraceptives, age at first live birth, number of live-born children, family history of breast- or ovarian cancer, and previous invasive cancer, but the results were virtually unchanged by further adjustment beyond age and calendar year. There was no clear difference in risk among seronegative RA, HR=0.77 (0.58-1.02), as compared with seropositive RA, HR=0.81 (0.67-0.98). Also, when the risk was assessed stratified by age at RA diagnosis, it was reduced for all age groups. When risks were assessed separately for each breast cancer stage, we noted reduced risks for all TNM stages. The risk was also reduced for both pre- and postmenopausal breast cancer.

The risk for incident RA was lower in women with a history of breast cancer, and similar to that of breast cancer in RA, fully adjusted OR=0.87 (95%CI 0.79-0.95). ORs stratified by seropositive or seronegative RA, and age at RA diagnosis, yielded similar results as

compared to the main analysis. There was no clear trend when examining the risk by age at breast cancer diagnosis. Also, there was no clear trend when examining the risk of RA by TNM-cancer stage, albeit missing information on cancer stage was substantial, especially among earlier cases of cancer.

During 2003-2016, there were 259 cases of breast cancer among RA patients, and 1499 cases among the controls. The OR for never (vs. ever) having received treatment with tamoxifen or AI (45% of RA cases, and 42% of controls), was 1.23 (95%CI 0.92-1.64)). Use of tamoxifen was somewhat more frequent than AI (n=629, vs n=565), with some overlap (n=184). The risk of developing RA among patients treated with both tamoxifen- and AI vs. never treated (fully adjusted OR=0.68 (95%CI 0.41-1.12). The risk among tamoxifen-only vs. never treated was OR=0.86 (95%CI 0.62-1.20), and among AI-only vs. never treated OR=0.97 (95%CI 0.69-1.37).

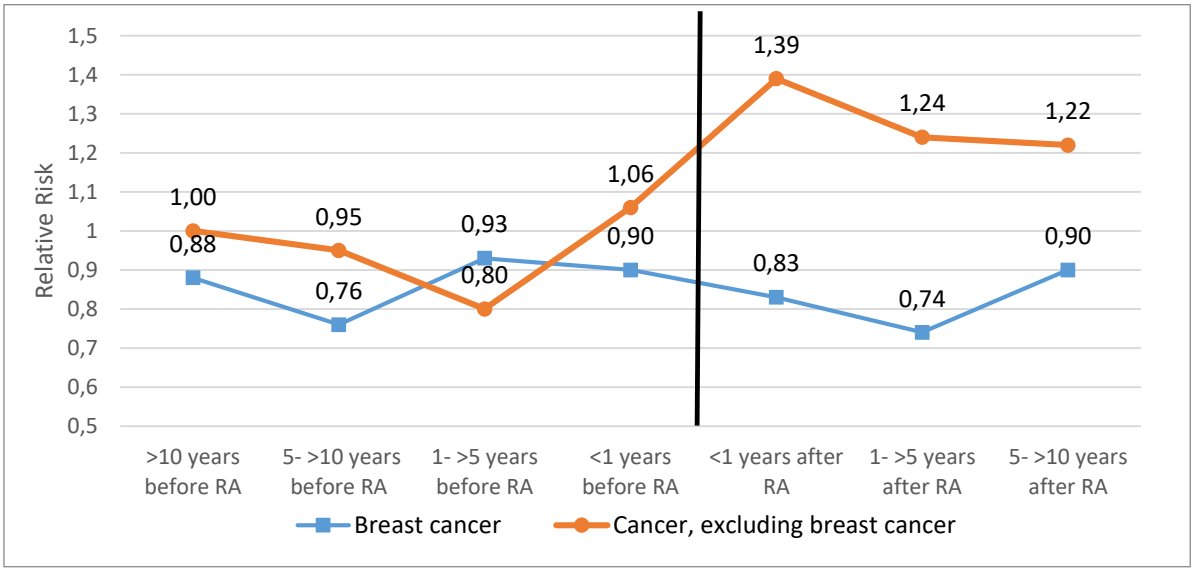

Figure 4.2. Relative risk of breast cancer other cancer in RA, as a function of time before (left of vertical line) and after (right of vertical line) RA diagnosis. RA vs. General population referents/controls, adjusted for age, country of birth and educational level

When examining cumulative tamoxifen exposure (years) we noted no trend in risk of later RA. For AI, we noted an increased risk of later RA among patients treated with AI for less than 6 months (OR=1.58 (95%CI 1.02-2.45), but also a decreased risk with longer exposure time (>24 months OR=0.57 (95%CI 0.39-0.82). Restricting the analysis to cancer cases occurring after the PDR was started (July 2005- Dec 2016) yielded similar results as compared with the main analysis. Likewise, excluding subjects with less than one year between the breast cancer diagnosis and index date, also provided results similar to the main analysis.

5 DISCUSSION

In this thesis, we have built upon previous knowledge and tried to further investigate and characterize the relationship between chronic inflammation, in the context of autoimmune rheumatic disease, and cancer. Using epidemiologic methods, we have shown that there is an increased risk of cervical neoplasia, albeit perhaps not invasive cancer, in women with RA, and, whether causal or not, that the risk is higher in patients treated with TNFi. Likewise, we have shown that women with SLE are at higher risk of developing cervical neoplasia, and that the risk is especially high in women treated with immunosuppressant therapy. Furthermore, we have added to the growing evidence of the short and medium term safety of TNFi, in terms of overall malignancies, and, albeit with less certainty, also found this to be true for tocilizumab, abatacept, and rituximab. We found a signal of an increased risk of squamous cell skin cancer for RA patients treated with abatacept. We have also shown that the risk of breast cancer for women with RA is reduced, and likewise that the future risk of RA in women with breast cancer is also reduced, and that these risk reductions did not seem to be explained by known breast cancer risk factors. Finally, we could not find evidence to support that tamoxifen, or AI, increases the risk of developing RA.

As has been described in this thesis, examining the risk of malignancies associated with rheumatic diseases and their treatments, is a complicated matter. Although observational studies are inherently equipped with significant limitations, they are the best option we currently have to answer these questions. RCTs are equipped with great strengths, such as a proper comparator that is balanced in terms of known, and unknown confounders. However, when examining rare long-term outcomes, several points argue against the use of RCTs. The patients that are presumably at the highest risk of developing cancer are often excluded, such as those with a previous malignancy, or those with anemia or other pathological lab-values of unknown origins. The study period is typically too short to investigate risks with long induction times, and open-label extensions lack a proper reference group. Other options, such as spontaneous reporting of adverse events by physicians, can detect important signals, but proper incidence rates cannot be computed due to large uncertainties in both the numerator (e.g. underreporting), and the denominator (unknown person-time at risk).

The fact that these are chronic conditions, use of the drugs in our studies will often be long-term, and in some cases lifelong. This highlights the importance of safety, and the need for long-term studies. Moreover, although it is comforting that there is only a minor risk increase of overall cancer in patients with RA, as we have seen in this thesis, this picture can be further nuanced. Cancer is a loaded term, but it can encompass everything from very mild disease that will have no detrimental effect on survival, to aggressive tumors that can cause sudden death. The lifetime risk of developing breast cancer for Swedish women is higher than 1 in 10, thus a 20% reduced risk will have a large impact (35). To further highlight the

clinical relevance we can compare this to cardiovascular risks in RA, which are well-known. For comparison, the risk of breast cancer in women 55-65 years old is 2-3 times higher than that of myocardial infarction. Unfortunately, given that there is only a minor risk increase for cancer overall, a lower risk of breast cancer, with a 5-year relative survival rate of 92%, means that there must be a higher risk for other cancers. For women, the 5-year relative survival for overall cancer is 74%, and for lung cancer, which is more common in patients with RA, it is an appalling 24% (35).

5.1 BDMARDS AND CANCER

Study III is one of the largest studies on the risk of malignant neoplasms in RA patients treated with bDMARDs to date. We found that there was no increased risk of solid, hematologic, or skin cancers with TNFi-treatment in RA. This was in line with the vast majority of previously published studies, including both RCTs and observational studies (63, 64). Our study added to this previous knowledge, and showed that the risk was still not increased in a more contemporary cohort, and with longer follow-up. Furthermore, there was no increased risk of overall malignancies in patients treated with other bDMARDs, with upper confidence limits ruling out clinically meaningful risk increases. These findings were in line with previous reports. However, before the publication of this study, there was limited data available from observational studies on the safety of non-TNFi bDMARDs, and most of data came from RCTs (80-82). We found no data on tocilizumab, but the limited observational data on rituximab, or abatacept, had shown no increased risk of overall malignancies (47, 83, 84). One of these studies found an increased risk of NMSC (which includes squamous cell skin cancer) in abatacept-treated, compared to methotrexate-treated, although based on only 5 events in the abatacept group. The only statistically significant risk increase we found in **Study III**, was that of invasive squamous cell cancer in abatacept-treated (fully adjusted HR=2.15 (95%CI 1.31-3.52)). Our result was attenuated by adjusting for confounders, and might be subject to residual confounding. Indeed, the age- and sex adjusted rates was considerably higher in all the RA exposure groups, compared to the general population referents. Studies published after **Study III** have confirmed the absence of an increased risk of overall cancer in RA patients treated with tocilizumab (159). Regarding abatacept, studies published after **Study III**, have both confirmed, and contradicted our results. Two recent studies utilizing data from different US claims- and healthcare databases, have found that abatacept initiation in RA was associated with a slightly increased risk of overall cancer (15-20%), with upper confidence limits below 1.4 (160, 161). The second of these two studies also found a 20% increased risk for NMSC in abatacept initiators, compared with other bDMARDs (161). However, as there were some noticeable baseline differences in both studies including comorbid conditions and baseline medications, between abatacept-, and other bDMARDs-treated, these results might be subject to residual confounding. Furthermore, identification of incident cancers, bDMARD-exposure and baseline comorbid conditions was limited to data that were captured in the medical record or claims. Another recent report from the observational US FORWARD study found no increased risk of overall malignancy for abatacept, compared to other bDMARDs or

csDMARDs (162). A collaborative effort using data from ARTIS, and the FORWARD study, and thus partly overlapping with other studies, as well as German, and Canadian data, found no risk difference for solid tumors, between abatacept and other bDMARDs (pooled estimate 1.0, 95%CI 0.8-1.3) (163). In **Study III**, we did not find a statistically significant risk increase for melanoma in abatacept initiators, although based on only 7 events, and the crude and adjusted rates was highest in this group. A recent publication conducted on WHO's global database of individual case safety reports (Vigibase®), found a 50% increased risk of reporting melanoma, but not overall cancer, in abatacept- compared to other bDMARDs-treated RA (164). As the authors discuss, this is consistent with the pharmacodynamic properties of abatacept, although this might perhaps lead to biased spontaneous reporting of events. In contrast to **Study III**, the Vigibase study was not able to adjust for any confounders, and as previously mentioned in this thesis, spontaneous reporting of adverse events leads to uncertainties in the person-time at risk. In conclusion, although there are question marks in terms of risk of cancer with abatacept-use, especially for skin cancers, most studies indicate that the short- and medium term risk of cancer is not increased.

5.2 CERVICAL NEOPLASIA

In **Study I** we made a series of important observations: There was a slightly elevated risk of cervical dysplasia, but not invasive cervical cancer, in biologics-naïve women with RA compared to the general population. The risk of HSIL, but not LSIL, was slightly higher in TNFi-treated, compared to biologics-naïve RA, and the risk of invasive cervical cancer was doubled. Furthermore, intensity of cervical screening was slightly higher in women with RA, but did not differ between TNFi-treated and biologics-naïve RA. In **Study II** we found that SLE is a risk factor for cervical neoplasia, overall, and for pre-malignant cervical lesions in particular. Additionally, we found that the risk is higher among those treated with systemic immunosuppressants, compared with antimalarials treated. We did not find evidence to support that there were any major differences in cervical screening that could explain these findings.

In **Study I** we found an increased risk of both HSIL and LSIL, but not of invasive cervical cancer, in biologics-naïve RA compared to general population comparators. However, the CIs for the different outcomes overlapped each other. Seeing as invasive cervical cancer was a rare outcome in our population of mostly screened Swedish women, the absence of an increased risk for cervical cancer in RA might thus be due to chance. If we combine HSIL and invasive cervical cancer, our results are similar to that of the study by Kim et al., which found a 50% increase of that outcome for women with RA, compared to women without systemic autoimmune disease (97). On the other hand, most previous studies on RA and invasive cervical cancer have found no association, the meta-analysis by Simon et al. reported an SIR of 0.87 (95% 0.72, 1.05) (46).

In **Study II** we found a doubled risk of cervical neoplasia in women with SLE, compared to the general population comparators. The risk was further doubled in women treated with immunosuppressants, compared to those treated with antimalarials. Our results were similar

to that of the study by Kim et al., which reported a 50-100% increased risk of HSIL and cervical cancer in women with SLE, compared to women without systemic autoimmune disease (97). Although most studies have found an increased risk of cervical dysplasia in women with SLE, the doubled risk we observed was a lot lower than the 9-fold risk increase reported in a meta-analysis by Zard et al. (102) However, the studies included were conducted in countries with very big differences in incidence and screening of cervical cancer compared to Sweden. We found no statistically increased risk of invasive cervical cancer, but the CI was too wide to rule out a clinically significant risk increase (HR=1.64, 95%CI 0.54-5.02). Several previous reports have found no significant risk increase in SLE (18, 103, 104). A Canadian cohort study with follow-up between 1975 and 1994, found an elevated risk for cervical cancer (SIR=8.15, 95% CI: 1.63–23.81). On the other hand, a large register-based study from California with follow-up between 1991 and 2002 reported an SIR of 0.55 (95%CI 0.39–0.75) (105). Many of the previous studies are quite old and have not taken cervical screening, or other potentially important confounders, into account. Results might therefore not be generalizable to present conditions, both in terms of management of SLE, and of cervical neoplasia. In a more similar setting to that of our study, a Danish study by Dreyer et al. found a doubled risk of cervical dysplasia in SLE. They also reported a doubled risk of HPV-associated cancers, but the study was not powered to rule in- or out clinically meaningful risk differences for invasive cervical cancer (SIR=0.6 (95%CI 0.1–4.5)) (165). In agreement with our findings, previous studies have found that treatment with immunosuppressants in SLE is associated with a higher risk of cervical dysplasia (166-168). A study based on US insurance data published after ours, compared the risk of HSIL or cervical cancer in women with SLE that initiated treatment with immunosuppressive drugs to that of antimalarials-treated, and found an HR of 1.40 (95% CI 0.92–2.12) (169) A register-based study from Denmark on women with autoimmune disease found a dose-dependent risk increase of cervical cancer with azathioprine, but no association with immunosupressants in general (103). Thus it seems like women with SLE treated with immunosuppressants are at a higher risk of cervical neoplasia, but whether this is due to the indication, or the exposure, is not clear.

As previously described in the background section, invasive cervical cancer is caused by persistent HPV infection, via precancerous dysplasia. The aim of cervical screening is to detect, and treat, pre-cancerous lesions before invasive cervical cancer develops. Almost all precancerous lesions that are diagnosed are detected through this screening process, and if left untreated, most of these lesions spontaneously regress. Thus a higher screening intensity will increase the incidence of cervical dysplasia, and decrease the incidence of invasive cervical cancer. On the other hand, a lower screening intensity will decrease the incidence of dysplasia, and increase the incidence of invasive cervical cancer. A recent study from the British biologics register found higher rates of LSIL, and lower rates of HSIL, in women with RA compared to the general population, which might be due to the higher rates of screening that they observed in women with RA (170). Our measure of screening intensity revealed similar rates of screening between women with RA, with or without TNFi treatment, and the

general population. In SLE, we noted some small numerical differences between SLE and the general population comparators, and between antimalarials- and immunosuppressants-treated SLE. With the high rates of cervical neoplasia in immunosuppressants-treated SLE in mind, it is somewhat worrying that we observed lower age-adjusted rates of screening in this group compared to antimalarials-treated, although not statistically significant. The differences in screening, in both **Study I** and **II**, might have been too small to explain differences in the crude rates of cervical neoplasia, and regression models were adjusted for previous screening. On the other hand, time to first screen might be too crude a measure to detect clinically meaningful differences in screening. A more thorough examination could perhaps reveal differences in the timing or the reasons for screening. For example, we did not discriminate between opportunistic or pre-planned screening. Our finding that women with SLE did not have lower rates of screening than the general population contrasts that of a Canadian study, which found a lower rate of self-reported cervical screening among women with SLE, compared to community rates (106). Likewise, some previous studies from the US have reported suboptimal screening in RA (108, 109). As previously mentioned, the study from British biologics register, found higher rates of cervical screening in women with RA, but lower rates in those with high HAQ-values (170). A register-based study conducted in Denmark, with a similar healthcare and cervical screening system to that of Sweden, observed similar screening rates among both SLE, and RA patients, as compared with the general population (103). Thus screening uptake in women with RA and SLE might differ between countries and might be dependent on patient disability.

The finding of an increased risk of invasive cervical cancer in TNFi-treated compared to biologics-naïve RA was a novel finding, and perhaps somewhat unexpected. Although there is a biologic rationale behind why TNFi could theoretically increase the risk of cervical cancer, previous studies on TNFi and aspects of cervical malignancy had shown no such association (53, 100, 101). The previous studies were perhaps not powered to rule out clinically significant risk increases, due to the low background risk of cervical cancer, and the fact that the latter two conditioned on a previous cervical lesion. Since **Study I** was published, a large US cohort study found a 1.3 times higher risk of the combined outcome of cervical dysplasia or cervical cancer, albeit not statistically significant, comparing bDMARD-treated to non-bDMARD-treated RA (171). Our finding of a doubled risk of invasive cervical cancer would correspond to one additional annual case for every 7000 treated women, which needs to be weighed against any benefit of TNFi treatment or its alternatives.

Comparing cancer risks between different RA treatments, over time and across different countries, is like trying to hit a moving target. The indication for bDMARD-treatments have widened over time. As shown by Figure 1.2, HAQ and DAS28 values in bDMARD-initiators have decreased over time. Also, non-bDMARD treatment patterns have changed, e.g. with the ascent of methotrexate as a cornerstone of RA treatment. This means that the cumulative exposure to other treatments in a biologics-naïve comparator, or previous and concomitant exposures in patients starting bDMARD-treatment, differ between modern cohorts and past cohorts. The use of biomarkers and criteria in diagnosing disease can also modify the

sensitivity or specificity of diagnosis, as well as the time point in the disease trajectory that the diagnosis is made. If, e.g. disease severity or disease duration is associated with the risk of developing cancer, this muddles the comparison of risk estimates in different studies. Thus, there might be powerful selection, to- and away from, different therapies, that is further complicated by changes over time. On this subject**,** an interesting observation in **Study I,** was that only 1 out of 14 cases of cervical cancer was reported in more contemporary initiators of TNFi (2006-). In the same analysis, all point estimates (LSIL, HSIL, and invasive cervical cancer) for TNFi moved towards lower risks, while all point estimates for the biologics-naïve cohort, compared to the general population, moved towards increased risks. In analogy to this, previous reports from ARTIS with follow-up through 2010 had found an increased risk of invasive melanoma in TNFi-treated vs. biologics-naïve RA (72). However, in **Study III,** with follow-up from January 2006 to December 2015, we found no risk difference between initiators of TNFi and biologics-naïve, with a point estimate that was below 1 (HR=0.84, 95%CI (0.60-1.18)). Admittedly, this could well be down to chance, or different biases. On the other hand, there is also the possibility that there has a been a shift, over time, in the channeling of patients at high risk of cervical neoplasia or melanoma, away from TNFi, and towards csDMARDs, and that our models were unable to fully handle this confounding by indication.

5.3 BREAST CANCER

The finding in **Study IV** of a 20% decreased risk of breast cancer in women with a history of RA, was in line with former studies, that had not adjusted for breast cancer risk factors (46). The risk of RA in women with a history of breast cancer was also reduced, in order of the same magnitude. No previous study had focused on this association, but a similar result was published as comparison in a study of the risk of lymphoma in RA, using the same Swedish registers, but with only partly overlapping data (early onset RA 1997-2006 vs. 2006-2016) (121). As previously mentioned, management of RA has evolved greatly over the last decades. New drugs have been introduced, and the approach to therapy has changed. There has been a shift in paradigm from “go low, go slow”, to aggressive early treatment with efficient DMARD therapy, with the goal of remission. During this period, mammographic screening for breast cancer has become well-established, partly reflected in a doubling of the age-standardized incidence of breast cancer in Sweden since the 1970-s (35). With this in mind, it’s remarkable how stable the relative risk of breast cancer in Nordic women with RA has remained. In a study on cancer risk in Swedish RA patients with follow-up from 1964-1984, the risk was 0.79 (0.6-1.0)(44), and in a study on Danish RA patients with follow-up from 1978-1991 the risk was 0.8 (0.7-0.9) (45). In another Swedish study with follow-up between 1990-2003, the risk was 0.83 (0.76-0.91) (42). **Study IV** had follow-up between 2006-2016, and found a 0.80 (0.68-0.93), with a similar decreased risk of RA in women with a history of breast cancer. Furthermore, there was no clear trend when examining TNM-stage of breast cancer, which could have reflected a detection bias. Taken together, this would argue against the hypothesis that the decreased risk of breast cancer in patients with RA is due to RA, or RA treatment.

Our models were adjusted for several potential confounders, including hormonal risk factors, but this had a very limited impact on the results. We observed that these risk factors were indeed risk factors for breast cancer in our study population, but they were only weakly associated with RA **(**Supplement **Study IV)**. If not due to these shared risk factors, although the possibility of unmeasured or residual confounding remains, shared genetics between RA and breast cancer would be another explanation. Some findings, including polymorphisms of cyclooxygenase-2 and DRB1, could perhaps partly explain the inverse association (172-174). However, without GWAS-studies, it's hard to quantify the net effects of these genetic factors. A perhaps noteworthy finding in **Study IV** was the similarity in breast cancer HR between seropositive RA, and seronegative RA, in terms of breast cancer risk. Seronegative RA is often thought of as a subset of RA with partly different etiology and presentation, and misclassification between seronegative RA and other conditions (including seropositive RA) is considered prevalent. Furthermore, an inverse association of the same magnitude has been reported between breast cancer and SLE (175). A study using GWAS-data could not find strong evidence for shared genetic causes as an explanation, albeit only 10 SLE-associated SNPs were investigated (176).

We examined the risk of developing future RA with tamoxifen- and AI-use, and in contrast to previous studies, we found no such association (143, 144). The study by Chen et al. included more than 200,000 cases of breast cancer, and found an increased risk of RA with both selective estrogen receptor modulators, including tamoxifen, and also with AI, compared to women with breast cancer who did not receive these treatments. Although the size of the study is impressive, some important limitations should be mentioned. Firstly, the study did not take follow-up time into account, if the mean time of follow-up differs between the groups then differences in the cumulative incidence might not reflect differences in the incidence rate. Secondly, they were unable to adjust for any confounders, most importantly age. Since the decision whether to administer treatment with tamoxifen or AI is affected by menopausal status and the age of the patient, and age is an important risk factor for RA, this might be an important confounder. The study by Caprioli et al. found an increased risk of RA among breast cancer patients treated with AI, compared to those treated with tamoxifen. However, they did not compare these rates to that of patients not treated with anti-estrogens or to that of the general population. The incidence rate of RA that they observed (4.33 per 1000 person-years), is somewhat lower than population-based age- and sex standardized incidence rates reported from Italy (127), and Sweden (1).

5.4 FURTHER METHODOLOGICAL CONSIDERATIONS

All four studies in this thesis were based on national registers with prospectively collected data with a high degree of validity and coverage. All cancer outcomes were identified independently of exposure and of the treating rheumatologist. We were able to account for TNM-cancer stage at diagnosis, which could reveal a potential detection bias. When assessing the risk of malignancies associated with different pharmaceutical treatments, we benchmarked these risks to matched general population comparator cohorts. When feasible,

we used active-comparator designs, which provides a more clinically relevant comparison and reduces confounding. Utilizing the rich source of data in the Swedish setting, we adjusted our models for several potentially important confounders, which were decided a priori. Diagnoses were identified using previously described, partly validated, algorithms.

Incomplete information concerning disease activity and disability, such as HAQ and DAS28 measures, was a limitation in **Studies I-III**. In **Study III** we could use the information in ARTIS to adjust for HAQ and DAS28 in comparisons between different bDMARD exposure categories, but not in comparisons with biologics-naïve RA. In **Study II**, although there are measures for monitoring of disease activity in SLE, we did not have this data. We lacked information on smoking and BMI, which could be potential confounders in all four studies. Adjustments for chronic obstructive pulmonary disorder in **Studies I and III** might capture some of the potential confounding due to smoking, but must be considered a poor proxy. On the other hand, previous reports from a Swedish RA study reported only minor differences in the prevalence of smoking between biologics-naïve-, and bDMARD-treated, RA (177). In **Study II**, we chose to perform a quantitative bias analysis on the potential impact of smoking. We found that even if we assumed extreme values for the prevalence of smoking among women with SLE, it could only explain part of the observed association. Another limitation was left truncation in the PDR (started in 2005), and in the outpatient-subset of the NPR (started in 2001). In **Study III**, we adjusted for sick-leave and disability pension at baseline with data from the Social Insurance Agency (Försäkringskassan). Short periods of sick-leave, less than 15 days, are not recorded and thus not accounted for in our analysis, because they are covered by the employer rather than the Social Insurance Agency. However sick-leave periods in RA are typically not short. A study from Finland published in 2006, with a similar social security system to that of Sweden, found that only 3.5% of sick leave periods in RA were 10-days or shorter (178)

In **Study IV** we did not have data on menarche, menopause or breastfeeding. We used age 50 as a proxy for menopause, which has been reported as the mean age of menopause in Swedish women, with a standard deviation of 3.77 (179). We did not account for HPV vaccination, which was introduced in 2006, during the study period of both **Studies I-II**. However, at the end of the study period, only about 2,5% of Swedish girls and women were vaccinated (180). In our study populations, consisting of mostly middle-aged women, penetrance would be expected to be even lower. Left truncation of the outpatient register could have resulted in misclassification of the disease under study or comorbidities. Furthermore, although coverage of prescribed drugs dispensed at a pharmacy is excellent, it typically does not capture drugs administered during a clinical visit. This means that coverage for infusion drugs such as rituximab, infliximab and cyclophosphamide, is presumably low. In **Studies I** and **III** we could identify these drugs in ARTIS. In **Study II,** where the study population consisted of SLE patients, this option was not available. However, since we grouped immunosuppressants together, and there was substantial overlap between immunosuppressant therapies, most of these patients would have been included under another drug. The fact that patients may have been exposed to multiple other pharmaceutical agents,

which may be associated with risk increases for malignancies that are not only short-term, prior to or after start of treatment of the drug under study made it hard to disentangle drug specific risks in **Studies I-III**. In **Study III**, 80% of the patients initiating treatment with other bDMARDs than TNFi had previously been treated with TNFi, and presumably failed on that treatment. We therefore defined an additional cohort of patients starting a new TNFi as their second ever bDMARD, as a perhaps more clinically relevant comparator. We also conducted analyses adjusted, or not, for previous TNFi-use, with similar results. However previous exposure to csDMARDs, could have varied between the groups, and this might be associated with long term effects on the outcome. The relatively recent introduction of non-TNFi bDMARDS, and to a lesser extent of TNFi, precluded analysis of long-term risks. Furthermore, our decision to group all TNFi together, with the bulk of the data coming from etanercept, adalimumab, and infliximab, might have concealed agent-specific risk differences in **Study I** and **III**. As a result of the nationwide design adopted in all studies in this thesis, we were able to assemble large study populations. Nevertheless, lack of statistical power in some cases forced us to study composite outcomes, and for some of the rare outcomes, such as invasive cervical cancer **(Studies I-II)**, and invasive melanoma **(Study III),** statistical power was indeed a limitation. It could be argued that some studies should be postponed until enough follow-up time has accrued to more definitely answer the specific research question. However, for serious adverse events, such as malignancies, the urgency might preclude further waiting, and even though estimates will be imprecise, even smaller studies may be able to rule out clinically meaningful risk increases.

6 CONCLUSIONS

Linkage of national Swedish registers and quality of care data provides a good platform for studying the occurrence of cancer in rheumatic disease, with patient populations of sufficient sizes to investigate even relatively rare outcomes. The richness of the data sources allows for detailed comparisons within treatment defined patient subgroups, which can address several potentially important sources of bias. Our findings may provide answers to a number of scientific questions, including both etiologic and exploratory questions. Specifically, we found that:

- Women with RA are at higher risk of cervical dysplasia, but perhaps not cervical cancer.
- Women with RA starting treatment with TNFi are at higher risk of cervical dysplasia and cervical cancer.
- Women with SLE are at higher risk of cervical neoplasia, in particular pre-malignant lesions. Those that are treated with immunosuppressants are at higher risk than those treated with antimalarials.
- Women with RA and SLE have similar rates of cervical screening as the general population. Screening does not seem to explain the higher rates of cervical dysplasia in RA and SLE.
- Patients with RA exhibit both higher and lower rates of site specific cancers but the net effect appears to be a slightly increased risk of overall cancer. The reasons behind these associations are not well established but are likely to involve causes related to both the disease and its treatment, as well as factors not directly related to RA.
- The overall risk of cancer among patients with RA initiating TNFi as first or second bDMARD, tocilizumab, abatacept, or rituximab does not differ substantially from that of biologic drug–naive, csDMARD-treated patients with RA. With some possible exceptions, bDMARDs appear safe in terms of cancer risks although site-specific risks are not well-examined, and long-term risks are still unknown.
- The risk of squamous cell skin cancer in RA patients starting treatment with abatacept is increased, a finding which calls for replication. Whether causal or not, caution is adviced for those with risk factors for skin cancer, and periodical skin examination could be warranted.
- There is a decreased risk of breast cancer in patients with RA, and a similar decrease in risk of RA in patients with a history of breast cancer. This does not seem to be readily explained by known risk factors for breast cancer. These findings suggest that other factors, independent of RA, drive the inverse association between the two diseases.
- Tamoxifen and AI as used in adjuvant breast cancer treatment does not seem to increase the short or medium term risk of RA. Long term risks, as well as the risk for inflammatory joint disease other than RA, are unknown.

7 FUTURE STUDIES

Although the studies described in this thesis have answered some important questions, it has also raised and highlighted some new questions. Here I have outlined some thoughts about future studies, some of which are already planned:

Studies I-II

Cervical cancer incidence in Sweden is low, and will hopefully continue to decrease due to HPV-vaccination and more efficient screening methods. However, globally it is still ranked 4th in cancer incidence in women, with more than half a million new cases every year. This means that cervical cancer as a comorbidity in rheumatic disease, will still be relevant for the foreseeable future. Although we did find an increased risk with TNFi in RA, this result calls for replication. As for the increased risk among immunosuppressants-treated in SLE, the extent to which this was caused by the medication, or the disease itself, was hard to disentangle. Future studies could address this issue in more detail. A greater understanding of these risks is also called upon in light of the fact that some guidelines now suggest more intensive screening in all women with SLE, and in some women with RA (181). Stressing the need for cervical screening in women potentially at increased risk seems justified, especially for those not adherent to screening guidelines. However, excessive screening can divert recourses away from more urgent needs, as well as cause unnecessary discomfort for the patient. Therefore, studies that can identify more specifically, in terms of e.g. disease severity or pharmaceutical agents, which women that we need to monitor more closely, are needed.

Study III

Although the evidence for short and medium term cancer risks with TNFi seems reassuring, owing to their recent introduction, long term risks are still inherently unknown. The question mark regarding the safety of abatacept in terms of risk for skin cancer, needs to be further investigated. As it stands, heightened surveillance or caution in patients at increased risk of skin cancer, e.g. those with a previous skin cancer, could be warranted. Furthermore, as new pharmaceutical agents are introduced in rheumatology, targeting new inflammatory pathways, the need for post-market surveillance studies continues.

Study IV

We found in this study that the risk of breast cancer was lower among women with RA, and that women with breast cancer had a lower risk of developing RA. We did not find evidence to support that this was due to socioeconomic- or parity- related factors. We did not investigate if the risk reduction was due to shared genetic factors between breast cancer and RA. Future studies examining the risk in siblings to patients with RA, or GWAS-studies, could help us further elucidate the origins of this association. Furthermore, although differential screening was not apparent when examining stage at detection between women with RA and population controls, this could not be ruled out, and should be examined in the future, incorporating mammographic screening, and mammographic density.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Syftet med den här avhandlingen var att fördjupa vår kunskap kring sambandet mellan reumatisk sjukdom, dess behandling, och cancer. Reumatisk sjukdom karaktäriseras av kronisk inflammation. Inflammation är immunförsvarets sätt att hantera kroppsfrämmande substanser eller organismer. Akut inflammation är ofta av godo, men kronisk inflammation tyder på att något har gått fel i immunförsvaret, att t.ex. immunförsvaret uppfattar kroppsegna substanser som främmande. Det har varit känt sedan 1800-talet att kronisk inflammation är kopplat till cancer och senare upptäckter har visat att det finns ett direkt orsakssamband mellan kronisk inflammation av många sorters ursprung, inklusive reumatisk sjukdom, och olika typer av cancer. Att studera sambandet mellan reumatisk sjukdom och cancer kompliceras av det faktum att det är svårt att bena ut vad som är orsakat av sjukdomen i sig, och vad som är orsakat av behandlingen. I slutet av 1900-talet började det komma nya sorters behandlingar som var riktade mot specifika komponenter i immunförsvaret, såsom signalmolekyler, istället för att slå brett på immunförsvaret. Ur biverkanssynpunkt är riktade behandlingar ofta att föredra, men behandlingar som riktar sig mot signalvägar som är inblandade i kroppens försvar mot cancertumörer kan vara förknippade med specifika biverkningar. Inom reumatologin kom de så kallade TNF-hämmarna under 90-talet som verkar på detta sätt, genom att blockera en signalmolekyl i immunförsvaret. Denna och andra behandlingar har visat sig mycket effektiva och har revolutionerat behandlingen av ledgångsreumatism. Problemet är att immunförsvaret är mycket komplext, vi vet helt enkelt inte riktigt vad som i övrigt sker i kroppen när vi går in och manipulerar dessa signalvägar och processer. Experimentella studier på t.ex. människoceller eller djur är en viktig pusselbit i jakten på en större förståelse, men det behövs även studier i levande människor. Randomiserade kliniska prövningar, där patienter slumpvis väljs ut till en behandling anses ha ett högt bevisvärde men lämpar sig av olika skäl dåligt för att studera ovanliga utfall som uppstår långt efter behandlingsstart. Därför måste vi ofta förlita oss på så kallade observationella studier, som utgår från vad som faktiskt har hänt i patientpopulationen, utan att manipulera exponeringen. I Sverige har vi en lång tradition av att samla information om invånarna i olika register, såväl demografiska som hälso- och sjukdomsregister. Denna avhandling har med epidemiologiska metoder, med hjälp av dessa register, undersökt risken för olika cancerformer bland patienter med ledgångsreumatism, och systemisk lupus erythematosus (SLE). Tack vare den rikliga informationen i dessa register kan vi identifiera dessa patientpopulationer, och jämförbara kontrollpopulationer från den övriga befolkningen. Vi kan följa dem över tid, från diagnos till eventuell cancer, migration, död o.s.v. Vi kan till detta addera information om vilka behandlingar som de har förskrivits utav läkare, eller hämtat ut på apotek. Genom att inkorporera information om t.ex. utbildningsnivå, sjukskrivning, eller annan samsjuklighet, kan vi justera för faktorer som kan tänkas störa skattningen av sambandet mellan reumatisk sjukdom, reumatisk behandling, och cancer.

I **Studie I** undersökte vi om behandling med TNF-hämmare hos patienter med ledgångsreumatism ökade risken för livmoderhalscancer, eller förstadier till

livmoderhalscancer. Då det finns möjlighet att screena för livmoderhalscancer undersökte vi dessutom i vilken utsträckning dessa patienter screenade sig. För dessa utfall jämförde vi denna grupp patienter med andra patienter med ledgångsreumatism som inte hade behandlats med TNF-hämmare. Dessutom jämförde vi dessa utfall mellan kvinnor med ledgångsreumatism som inte hade behandlats med TNF-hämmare, med matchade kontroller från den övriga befolkningen. Vi kontrollerade för flera potentiella störfaktorer, såsom ålder, utbildningsnivå, civilstånd, tidigare screening, andra sjukdomar och sjukvårdsanvändning. Vi fann en 40-50% ökad risk för förstadier till livmoderhalscancer, men inte för faktisk livmoderhalscancer, hos kvinnor med ledgångsreumatism som inte hade behandlats med TNF-hämmare, jämfört med befolkningskontroller. Vi fann även att dessa kvinnor screenade sig i större utsträckning än kontrollerna, men skillnaden var endast marginell. För patienter behandlade med TNF-hämmare fann vi en 20-40% ökad risk för förstadier till livmoderhalscancer, samt en dubblad risk för faktisk livmoderhalscancer, jämfört med övriga ledgångsreumatiker. Vi fann ingen nämnvärd skillnad i screening mellan de två patientgrupperna. En ökad risk för livmoderhalscancer förknippad med TNF-hämmare har inte rapporterats från andra studier. Även om vi kunde justera för många potentiellt viktiga störfaktorer, så kan riskökningen ändå vara ett resultat av kvarvarande systematiska fel eller helt enkelt vara ett slumpfynd. Vi var därför försiktiga i vår tolkning av detta fynd.

I **Studie II** var syftet att studera risken för förstadier till livmoderhalscancer, och faktisk livmoderhalscancer, samt följsamhet till screening, bland kvinnor med SLE, överlag och i relation till SLE-behandling, och att jämföra denna risk med befolkningskontroller, samt att även undersöka följsamheten till screening. Genom att länka olika register kunde vi identifiera en grupp kvinnor med SLE, dela upp denna grupp i två subgrupper baserade på hur aggressiv behandling de erhöll, och även identifiera matchade befolkningskontroller. Vi kontrollerade våra analyser för möjliga störfaktorer, såsom ålder, utbildningsnivå, sjukvårdsanvändning, civilstånd, antalet barn, och tidigare screening. Vi fann en fördubblad risk för förstadier till-, eller faktisk livmoderhalscancer, bland kvinnor med SLE jämfört med kontroller. Vi fann att risken var ännu högre bland de patienter som erhållit mer aggressiv behandling. Följsamheten till screening skiljde sig inte nämnvärt åt mellan grupperna. Vi kunde inte bena ut om den höga risken i gruppen med mer aggressiv behandling berodde på behandlingen, eller på sjukdomen i sig. Vi drog dock slutsatsen att oavsett detta så är det av vikt att kvinnor med SLE skyddas mot cervixcancer genom screening och vaccinering.

I **Studie III** undersökte vi risken för cancer bland ledgångsreumatiker som behandlats med TNF-hämmare, eller med tre andra nya riktade läkemedel (abatacept, rituximab, och tocilizumab), och jämförde den med patienter med ledgångsreumatism som inte hade behandlats med dessa läkemedel. Gruppen som behandlats med TNF-hämmare delades upp i dem som behandlades med en första-, eller en andra-, TNF-hämmare. Dessa fem grupper av behandlingsdefinierade patientgrupper jämfördes mot patienter som behandlats med preparat av den äldre sorten. Vi undersökte risken för cancer generellt, men även uppdelat på blodcancer, solida tumörer, skivepitelcancer i huden, samt malignt melanom i huden. Liksom i föregående studier så kontrollerade vi för potentiellt viktiga störfaktorer, såsom ålder, kön,

utbildningsnivå, samt olika mått på samsjuklighet, behandling och sjukvårdsutnyttjande, smat även sjukskrivning och förtidspension. Med undantag för en ökad risk för skivepitelcancer i huden bland de som hade behandlats med abatacept, fann vi ingen säker skillnad i cancerrisk mellan grupperna. När vi kontrasterade gruppen ledgångsreumatiker mot befolkningskontroller såg vi dock att dessa hade en något ökad risk för cancer generellt, i linje med tidigare studier. Vi drog slutsatsen att cancerrisken på kort-, och medellång sikt, med användning av dessa preparat förefaller inte vara ökad, möjligtvis med undantag för abatacept och skivepitelcancer i huden.

Tidigare studier som går tillbaka ända till 1960-talet har konstant visat på en lägre risk för bröstcancer bland kvinnor med ledgångsreumatism. Dessa studier har dock aldrig försökt bena ut vad denna risk beror på. I **Studie IV** försökte vi därför undersöka om vi fortsatt såg en minskad risk för bröstcancer i denna patientgrupp med beaktande av kända riskfaktorer för bröstcancer. Vi undersökte även om risken för att utveckla ledgångsreumatism bland kvinnor med bröstcancer avvek från den i övriga befolkningen. Då tidigare rapporter har pekat på en ökad risk för ledgångsreumatism bland kvinnor som behandlats med antihormonell bröstcancerbehandling, försökte vi även undersöka detta. Med hjälp av register så identifierade vi nyinsjuknade kvinnor med ledgångsreumatism, och matchade befolkningskontroller. I våra modeller tog vi förutom demografiska och socioekonomiska faktorer, även barnafödande och hormonell behandling (p-piller eller östrogensubstitution i samband med klimakteriet) i beaktning. Vi fann att risken för bröstcancer fortfarande var 20% lägre bland kvinnor med ledgångsreumatism men vi kunde inte förklara denna skillnad genom skillnader i de faktorer vi kontrollerade för. Vi fann även att risken för att insjukna i ledgångsreumatism var lägre bland kvinnor med tidigare bröstcancer. Detta kan tyda på att det finns andra gemensamma faktorer mellan dessa sjukdomar, som vi inte har kontrollerat för, som medför en invers association mellan dessa och som inte har med själva sjukdomarna eller deras behandlingar att göra. Till slut fann vi också att i motsats till tidigare studier var antihormonell behandling mot bröstcancer inte förknippad med en ökad risk för att utveckla ledgångsreumatism.

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